Curcumin inhibits prostate cancer metastasis in vivo by targeting the inflammatory cytokines CXCL1 and -2.

Killian PH, Kronski E, Michalik KM, Barbieri O, Astigiano S, Sommerhoff CP, Pfeffer U, Nerlich AG, Bachmeier BE.

Institute of Laboratory Medicine (former Dept. of Clin. Chemistry and Biochemistry), Ludwig-Maximilians-University, Munich, Germany.

Abstract

In America and Western Europe, prostate cancer is the second leading cause of death in men. Emerging evidence suggests that chronic inflammation is a major risk factor for the development and metastatic progression of prostate cancer. We previously reported that the chemopreventive polyphenol curcumin inhibits the expression of the proinflammatory cytokines CXCL1 and -2 leading to diminished formation of breast cancer metastases. In this study, we analyze the effects of curcumin on prostate carcinoma growth, apoptosis and metastasis. We show that curcumin inhibits translocation of NFκB to the nucleus through the inhibition of the IκB-kinase (IKKβ), leading to stabilization of the inhibitor of NFκB, IκBα, in PC-3 prostate carcinoma cells. Inhibition of NFκB activity reduces expression of CXCL1 and -2 and abolishes the autocrine/paracrine loop that links the two chemokines to NFκB. The combination of curcumin with the synthetic IKKβ inhibitor, SC-541, shows no additive or synergistic effects indicating that the two compounds share the target. Treatment of the cells with curcumin and siRNA-based knockdown of CXCL1 and -2 induce apoptosis, inhibit proliferation and downregulate several important metastasis-promoting factors like COX2, SPARC and EFEMP. In an orthotopic mouse model of hematogenous metastasis, treatment with curcumin inhibits statistically significantly formation of lung metastases. In conclusion, chronic inflammation can induce a metastasis prone phenotype in prostate cancer cells by maintaining a positive proinflammatory and prometastatic feedback loop between NFκB and CXCL1/-2. Curcumin disrupts this feedback loop by the inhibition of NFκB signaling leading to reduced metastasis formation in vivo.