Coupling to a glioblastoma-directed antibody potentiates anti-tumor activity of curcumin.


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Abstract

Current therapies for glioblastoma are largely palliative, involving surgical resection followed by chemoradiation therapy, which yield serious side effects and very rarely produce complete recovery. Curcumin, a food component, blocked brain tumor formation but failed to eliminate established brain tumors in vivo, probably because of its poor bioavailability. In the glioblastoma GL261 cells, it suppressed the tumor-promoting proteins NF-κB, P-Akt1, VEGF, Cyclin D1, and BCl_2 and triggered cell death. Expression of exogenous p50 and p65 subunits of NF-κB conferred partial protection on transfected GL261 cells against curcumin insult, indicating that NF-κB played a key role in protecting glioblastoma cells. To enhance delivery, we coupled curcumin to the glioblastoma-specific CD68 antibody in a releasable form. This resulted in a 120-fold increase in its efficacy to eliminate GL261 cells. A very similar dose response was also obtained with human glioblastoma lines T98G and U87MG. GL261-implanted mice receiving intra-tumor infusions of the curcumin-CD68 adduct followed by tail-vein injections of solubilized curcumin displayed a 4-5-fold reduction in brain tumor load, survived longer, and about 10% of them lived beyond 100 days. Hematoxylin-eosin staining of brain sections revealed a small scar tissue mass in the rescued mice, indicating adduct-mediated elimination of glioblastoma tumor. The tumor cells were strongly CD68+ and microglial cells in the tumor periphery were strongly positive for microglial Iba1, but weakly positive for CD68. This strategy of antibody-targeting of curcumin to tumor comes with the promise of yielding a highly effective therapy for glioblastoma brain tumors. © 2013 Wiley Periodicals, Inc.

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