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Down-regulation of tissue inhibitor of metalloproteinases-1 in gliomas: a new marker of cannabinoid antitumoral activity?

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Abstract

Cannabinoids, the active components of *Cannabis sativa* L. and their derivatives, inhibit tumor growth in laboratory animals by inducing apoptosis of tumor cells and inhibiting tumor angiogenesis. It has also been reported that cannabinoids inhibit tumor cell invasiveness, but the molecular targets of this cannabinoid action remain elusive. Here we evaluated the effects of cannabinoids on the expression of tissue inhibitors of metalloproteinases (TIMPs), which play critical roles in the acquisition of migrating and invasive capacities by tumor cells. Local administration of Delta(9)-tetrahydrocannabinol (THC), the major active ingredient of cannabis, down-regulated TIMP-1 expression in mice bearing subcutaneous gliomas, as determined by Western blot and immunofluorescence analyses. This cannabinoid-induced inhibition of TIMP-1 expression in gliomas (i) was mimicked by JWH-133, a selective CB(2) cannabinoid receptor agonist that is devoid of psychoactive side effects, (ii) was abrogated by fumonisin B1, a selective inhibitor of ceramide synthesis de novo, and (iii) was also evident in two patients with recurrent glioblastoma multiforme (grade IV astrocytoma). THC also depressed TIMP-1 expression in cultures of various human glioma cell lines as well as in primary tumor cells obtained from a glioblastoma multiforme patient. This action was prevented by pharmacological blockade of ceramide biosynthesis and by knocking-down the expression of the stress protein p8. As TIMP-1 up-regulation is associated with high malignancy and negative prognosis of numerous cancers, TIMP-1 down-regulation may be a hallmark of cannabinoid-induced inhibition of glioma progression.

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