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ORIGINAL RESEARCH

Chrysin suppresses proliferation, migration, and invasion in glioblastoma cell lines via mediating the ERK/Nrf2 signaling pathway

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Background: Chrysin, an active natural bioflavonoid, has been proven to protect against carcinogenesis. However, the role of chrysin in glioblastoma and the potential molecular mechanisms remain to be elucidated. In our previous study, we found that nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) is highly expressed in a variety of glioblastoma cell lines associated with the mitogen-activated protein kinase (MAPK) pathway. The aim of this study was to evaluate the antitumor effects of chrysin in glioblastoma cells and how chrysin is related to the MAPK/Nrf2 signaling pathway.

Methods: A Cell Counting Kit-8 assay and a plate colony formation assay were performed to evaluate cell proliferation. Cell migration ability was tested by a wound-healing assay. Transwell migration and Matrigel invasion assay were used to test the migration and invasion potential of cells. Nrf2 was knocked down by shRNA transfection. Protein expression was determined by Western blotting and immunofluorescence staining. The *in vivo* anticancer effect was measured using tumor xenografts in nude mice.

Results: Chrysin inhibited the proliferation, migration, and invasion capacity of glioblastoma cells in dose- and time-dependent manners. Mechanistically, chrysin deactivated the Nrf2 signaling pathway by decreasing the translocation of Nrf2 into the nucleus and suppressing the expression of hemeoxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase-1, meanwhile, Nrf2 shRNA attenuated the anticancer activity of chrysin. Furthermore, chrysin downregulated the protein expression of p-extracellular signal-regulated kinase 1 and 2 (ERK1/2), but did not significantly affect p-JNK and p-P38 expression levels. However, the downregulated level of Nrf2 and the antitumor effect of chrysin in glioblastoma cell lines were partially abrogated by the ERK1/2 signaling inhibitor (U0126). Finally, chrysin inhibited tumor growth in U87 xenografts.

Conclusion: Our results show that chrysin exerts anticancer activity in glioblastoma cell lines possibly via the ERK/Nrf2 signaling pathway and indicate the potential application of chrysin as a natural sensitizer in chemotherapy.

Keywords: chrysin, glioblastoma, nuclear factor erythroid 2-related factor 2, Nrf2, extracellular signal-regulated kinase, ERK

Introduction

Glioma is the most common form of primary central nervous system tumors in adults. According to the classification of the World Health Organization (WHO), glioblastoma multiforme (GBM), described as grade IV glioma, is the most frequent and malignant histological subtype.¹ Standard treatments for GBM for disease-free survival in randomized studies include reasonable surgical resection, radiotherapy, and chemotherapy with temozolomide.² Despite decades of efforts and advances in

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