

Levetiracetam enhances the Temozolomide effect on glioblastoma stem cell proliferation

Bianca Maria Scicchitano, Silvia Sorrentino, Gina Lama and Gigliola Sica

Istituto di Istologia e Embriologia. Università Cattolica del Sacro Cuore, Roma, Italia

Glioblastoma Multiforme (GBM) is a highly aggressive brain tumor in which cancer cells with stem cell-like features, called Cancer Stem Cells (CSCs), were identified. CSCs show a high capacity to resist to standard therapies, finally leading to a poor prognosis. Thus, the development of efficient strategies targeting these cells are urgently needed. We have previously demonstrated the presence of two CSC populations in GBM, one derived from the GBM area called enhanced lesion (GCSC) and the other one from the brain area adjacent to the tumor margin (PCSC), that greatly differ in their growth properties and tumor-initiating ability. Tumor recurrence occurs in tissue neighboring GBM suggesting a growing relevance for this area in translational research. To date the most effective chemotherapies to treat GBM are alkylating agents such as temozolomide (TMZ). Epigenetic mechanisms are increasingly recognized as a major factor contributing to pathogenesis of cancer including glioblastoma. Histone deacetylase (HDAC) inhibitors can interfere with TMZ activity by modulating methylguanine methyltransferase (MGMT) expression, resulting in increased TMZ efficacy. Levetiracetam (LEV), an antiepileptic drug, is known to modulate the transcription of HDAC, ultimately silencing MGMT. Since TMZ is the chemotherapeutic agent most widely used in newly diagnosed adult glioblastoma patients, we evaluated its effects on the proliferation rate of both GCSC and PCSC deriving from five patients, in comparison with the effects of other drugs such as etoposide, irinotecan and carboplatin. Our results demonstrated that TMZ was the less efficient agent, hence we verified the possibility to increase the effect of TMZ by combining it with LEV. Here we show that LEV significantly enhances the inhibitory effect of TMZ on the proliferation of the GCSC deriving from four patients and of the PCSC deriving from two patients. This effect seems to be mediated by HDAC6 since its expression is up-regulated in the TMZ resistant cells and correlates with MGMT expression. Taken together our results suggest that GCSC and PCSC differ in their ability to respond to the combined chemotherapeutic treatment we used and that the manipulation of HDAC6 expression might be a potential strategy for treating glioblastoma and overcoming resistance to TMZ.

Keywords

Glioblastoma, Cancer Stem Cells, Chemotherapeutic drugs, Temozolomide, Epigenetic modifications, Levetiracetam