Molecular Neurobiology (2018) 55:6816–6833
https://doi.org/10.1007/s12035-018-0895-1

Combination Therapy with Sulfasalazine and Valproic Acid Promotes Human Glioblastoma Cell Death Through Imbalance of the Intracellular Oxidative Response

Carlos Gustavo Garcia[1] · Suzana Assad Kahn[2] · Luiz Henrique Medeiros Geraldo[2] · Igor Romano[1] · Ivan Domith[1] · Deborah Christinne Lima e Silva[1] · Fernando dos Santos Assunção[2] · Marcos José Ferreira[3] · Camila Cabral Portugal[4] · Jorge Marcondes de Souza[5] · Luciana Ferreira Romão[2] · Annibal Duarte Pereira Netto[3] · Flávia Regina Souza Lima[2] · Marcelo Cossenza[1,6]

Received: 6 July 2017 / Accepted: 9 January 2018 / Published online: 19 January 2018

Abstract

Glioblastoma (GBM) is the most common and aggressive malignant primary brain tumor and still lacks effective therapeutic strategies. It has already been shown that old drugs like sulfasalazine (SAS) and valproic acid (VPA) present antitumoral activities in glioma cell lines. SAS has also been associated with a decrease of intracellular glutathione (GSH) levels through a potent inhibition of xc- glutamate/cystine exchanger leading to an antioxidant deprotection. In the same way, VPA was recently identified as a histone deacetylase (HDAT) inhibitor capable of activating tumor suppression genes. As both drugs are widely used in clinical practice and their profile of adverse effects is well known, the aim of our study was to investigate the effects of the combined treatment with SAS and VPA in GBM cell lines. We observed that both drugs were able to reduce cell viability in a dose-dependent manner and the combined treatment potentiated these effects. Combined treatment also increased cell death and inhibited proliferation of GBM cells, while having no effect on human and rat cultured astrocytes. Also, we observed high protein expression of the catalytic subunit of xc- in all the examined GBM cell lines, and treatment with SAS blocked its activity and decreased intracellular GSH levels. Noteworthy, SAS but not VPA was also able to reduce the [^{14}C]-ascorbate uptake. Together, these data indicate that SAS and VPA exhibit a substantial effect on GBM cell's death related to an intracellular oxidative response imbalance, making this combination of drugs a promising therapeutic strategy.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12035-018-0895-1) contains supplementary material, which is available to authorized users.

✉ Marcelo Cossenza
mcossenza@gmail.com

[1] Program of Neurosciences, Institute of Biology, Fluminense Federal University, Niterói, RJ, Brazil

[2] Program of Cell Biology and Development, Institute of Biomedical Sciences, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

[3] Program of Chemistry, Institute of Chemistry, Federal Fluminense University, Niterói, RJ 24020-141, Brazil

[4] Instituto de Investigação e Inovação em Saúde (i3S) and Instituto de Biologia Molecular e Celular (IBMC), Universidade do Porto, Porto, Portugal

[5] Service of Neurosurgery, Division of Neurosurgery, Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

[6] Department of Physiology and Pharmacology, Biomedical Institute, Fluminense Federal University, Hernani Pires de Mello Street, 101, 24210-130, Niteroi, Rio de Janeiro, Brazil

Keywords xCT · Glioma · Glutathione · Reactive oxygen species · Ascorbate

Introduction

Malignant gliomas are the most common primary central nervous system (CNS) tumors in adults and comprise a group of extremely heterogeneous tumors with glial origin. Glioblastoma (GBM, WHO Grade IV Astrocytoma) is the most aggressive glial tumor, accounting for more than 50% of the malignant gliomas. This astrocyte-derived tumor presents a very invasive, angiogenic, and proliferative behavior and is characterized by its cellular and genetic heterogeneity [1–4]. Despite the aggressive standard treatment with surgical resection and radiotherapy with concurrent and adjuvant chemotherapy with Temozolomide (a DNA alkylating agent), virtually all patients evolve with early tumor recurrence, leading newly diagnosed patients to a poor overall survival of 14.6 months. Although novel approaches such anti-angiogenic agents (Bevacizumab), new chemotherapy