STRATAGEM
CA17104

ABSTRACT BOOK

COST Action 17104 (STRATAGEM) WG3 Meeting - International Online Symposium on "New Therapeutic Tools Against Preclinical Models of Multidrug Resistant Tumors"
4th November 2020

cost
EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

COST is supported by the EU Framework Programme
Horizon 2020

Novel TrxR1 inhibitors induce oxidative stress and sensitize human multidrug resistant glioblastoma cells to chemotherapy

Ana Podolski-Renić, Mirna Jovanović, Miodrag Dragoj, Jelena Dinić, Sofija Jovanović Stojanov, Milica Pešić

[1] Institute for Biological Research "Siniša Stanković" (IBISS) – National Institute of Republic of Serbia, University of Belgrade, Serbia

*Corresponding author: ana.podolski@ibiss.bg.ac.rs

Glioblastoma (GBM) is the most common malignant brain tumor in adults, with limited treatment options due to aggressive invasiveness and resistance to therapy. Developing novel strategies for GBM treatment is of pivotal importance. Elevated expression of antioxidant defense system components thioredoxin (Trx) and thioredoxin reductase (TrxR) is a common feature of cancer cells and correlates with cancer progression and poor prognosis. We evaluated anticancer properties of novel TrxR1 inhibitors (DVD-444 and DVD-445) in human sensitive glioblastoma cell line and corresponding multidrug resistant (MDR) cell line (U87and U87-TxR, respectively).

Compounds DVD-444 and DVD-445 showed a similar growth inhibitory effect in U87 and U87-TxR cells. Both compounds were less effective in peripheral blood mononuclear cells showing selectivity towards cancer cells. Significant elevation of RONS level after treatment with TrxR1 inhibitors was observed only in MDR glioblastoma cells. However, DVD-444 and DVD-445 induced changes in expression of antioxidant enzymes in both cell lines, implying the existence of oxidative stress inside the cells. Besides antioxidative effect, DVD-444 and DVD-445 decreased cell proliferation and suppressed invasion and migration of glioblastoma cells. Both TrxR1 inhibitors increased accumulation of P-glycoprotein substrate Rho123 in U87-TxR cells. Furthermore, the compounds showed potential to modulate MDR by sensitizing U87-TxR cells to paclitaxel.

In conclusion, we found that novel TrxR1 inhibitors induced oxidative stress, leading to changes in expression of antioxidant enzymes. Consequently, these inhibitors affected cell proliferation and suppressed invasion and migration of glioblastoma cells. Moreover, TrxR1 inhibitors were capable to overcome MDR. Considering the fact that drug resistance and invasion are the main causes of ineffective GBM treatment, novel TrxR1 inhibitors, particularly DVD-444, could be valuable candidates for new GBM treatment strategy.