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REGULATION OF GLYCOLYSIS-RELATED GENES EXPRESSION IN U87 ERN1 KNOCKDOWN GLIOMA CELLS

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Introduction. Glioma cells are enhanced by glycolytic activity irrespective of the supply of oxygen. This leads to an increase of cell proliferation performed through the formation of intermediates. ER (Endoplasmic reticulum) stress as well as hypoxia and ischemia are important factors influencing tumor cells proliferation and survival, responsible for metabolism reprogramming mainly through ERN1(endoplasmic reticulum to nuclei-1) signaling enzyme. Goal of this study was to investigate the expression level of *GPI*, *GNPDA1*, *ALDOA*, *ALDOC*, *ENO1* and *ENO2* genes in glioma U87 cells upon hypoxia and ischemia, to evaluate their role in glioma cells proliferation through ERN1 mediated signaling.

Methods. Human glioma cell line U87 and its subline with complete suppression of ERN1 enzymatic activities were used. Expression of glycolysis-related genes was measured in glioma cells using qPCR. Hypoxic condition was created in incubator with 3% oxygen and 5% carbon dioxide levels. Culture plates were exposed to this condition for 16 h. Cells were also cultivated in DMEM without glucose or glutamine for glucose and glutamine deprivation.

Results and Discussion. We have demonstrated that the expression of genes encoding GPI, ALDOA, ALDOC, ENO1 and ENO2 enzymes is increased (+30%, +28%, +822%, +25% and +272%, respectively) in glioma cells with totally suppressed enzymatic activity of ERN1 (dnERN1), being more intense for *ALDOC* and *ENO2* genes. It is also increased (+49%, +33%, +16%, +27% and +252%) in glioma U87 cells when only endoribonuclease activity of ERN1 signaling enzyme is suppressed (dnr-ERN1). Tunicamycin-induced ER stress decreases (-22% and -40%) the expression level of *ALDOC* and *ENO2* genes in glioma cells without endoribonuclease activity of ERN1, but does not significantly change the expression level of *GPI*, *GNPDA1*, *ALDOA* and *ENO1* mRNAs.

Multidirectional changes have been demonstrated for expression levels of *GPI*, *GNPDA1*, *ALDOA*, *ALDOC*, *ENO1* and *ENO2* mRNAs both in wild type glioma cells and in cells with totally suppressed enzymatic activity of ERN1 under glutamine and glucose deprivation as well as hypoxia. Furthermore, ERN1 knockdown modifies effects of hypoxia as well as glutamine and glucose deprivations on the expression of most studied genes.

Conclusions. Results of this investigation clearly demonstrate that the level of glycolysis-related genes expression depends on ERN1 enzymatic activity as well as on hypoxic and ischemic conditions and that the expression of *GPI*, *ALDOC*, and *ENO2* genes can contribute to the suppression of glioma cell proliferation introduced by downregulation of ERN1 signaling enzyme function.

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