increased pneumosphere-forming capacity and efficiency of toluidine blue elimination. In addition, Ruk/CIN85 expression levels in H69 and MOR cells with therapeutic resistance to cisplatin and doxorubicin respectively were up to 10 times higher in comparison with their parental cells.

Together, the data obtained suggest that high level of adaptor protein Ruk/CIN85 plays a key regulatory role in the induction of EMT in non-small-cell lung carcinoma, thus opening new opportunities for therapeutic intervention.

MOLECULAR MECHANISMS OF DEPENDENCE OF HYPOXIC REGULATION ON ENDOPLASMIC RETICULUM STRESS

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Hypoxia is one of the compulsory factors for malignant growth. Condition is realized by the transcription factor – hypoxia-inducible factor (HIF). HIF activates the transcription of genes that play a decisive role in the biology of cancer, including angiogenesis, cell proliferation and survival, glucose metabolism, and invasion. The endoplasmic reticulum is key to the response of the cell to hypoxia inducing stress of the endoplasmic reticulum. The ERN1 (from endoplasmic reticulum to nucleus signaling 1) signaling pathway controls the expression of a large group of genes that dependent on the endoplasmic reticulum stress and hypoxia. The X-box binding protein 1 (XBP1) is a key component of the ERN1 signaling pathway and controls about a thousand genes responsible for tumor growth, including most of the hypoxia-induced genes.

The goal of our study was to evaluate the effect of hypoxia on the expression of genes in relation to the inhibition of the ERN1 pathway. Namely, to determine the level of gene expressions associated with glioma growth in relation to the IRE1 signaling pathway inhibition; identify binding sites for XBP1 and HIF transcription factors in the promoter region of a subset of nuclear genes encoded mitochondrial proteins.

Bioinformatics methods for identification of HIF- and XBP1-binding sites in the promoter region of cancer growth-related genes were used. We used two sublines of line U87: control glioma cells and cells with blockade of ERN1 function by dominant/negative cDNA-construct. For this study we select next genes: *ME2* (malic enzyme 2), *NNT* (nicotinamide nucleotide transhydrogenase), *IDH2* (isocitrate dehydrogenase ($NADP^+$) 2, mitochondrial), *MDH2* (malate dehydrogenase 2), *GOT2* (glutamate oxaloacetate transaminases), *FAM16A* (family with sequence similarity 162 member A), *ENDOG* (endonuclease G), and *AIFM1* (apoptosis-inducing factor mitochondria associated 1). The expression level of studied genes was determined in glioma cells by real-time quantitative polymerase chain reaction. Statistical analysis was performed according to Student's *t*-test using Excel program.

We have studied the effect of hypoxia on the expression level of glioma growth-related genes such as *ME2, NNT, IDH2, MDH2, GOT2, FAM16A, ENDOG,* and *AIFM1* in relation to inhibition of the endoplasmic reticulum stress mediated by ERN1 signaling. It was shown that the expression level is significantly down-regulated in glioma cells without ERN1 enzyme function, except *IDH2, NNT, ENDOG,* and *FAM162A* genes, which expression level is strongly up-regulated. At the same time, inhibition of ERN1 leads to down-regulation of the expression level of *AIFM1* gene, which is involved in apoptosis and autophagy signaling pathways. We have shown that hypoxia affects the expression level of most studied genes in gene-specific manner and that effect of hypoxia on the expression of some genes is modulated by ERN1. Binding sites for HIF and XBP1 were found in most studied genes, and some of these binding sites can recognize both transcription factors.

The expression of all studied genes is responsible for ERN1 signaling enzyme function in gene-specific manner, because inhibition of IRE1 significantly affects their expression. Results of our investigation demonstrate that hypoxia may affect the expression of genes through binding sites for HIF and XBP1. Therefore, ERN1 can modify the effect of hypoxia on numerous gene expressions through induction of XBP1 and interaction of HIF and XBP1 transcription factors in promoter at both different and same binding sites.

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