Plentiful studies have proven the connection between endoplasmic reticulum stress and malignant growth [1–4]. Neoplasms use signaling pathways of endoplasmic reticulum stress response to adapt and to enhance tumor cells proliferation under unfavorable environmental conditions [5–7]. It is well known that activation of IRE1/ERN1 (inositol requiring enzyme 1/endoplasmic reticulum to nucleus signaling 1) branch of the endoplasmic reticulum stress response under certain circumstances may lead to apoptosis and to cell death, and suppression of its function significantly inhibits glioma growth [8–11]. Glucose and glutamine are substrates for glycolysis and glutaminolysis. These key metabolic pathways participate in cell cycle control at multiple points and thus are of importance for tumor progression [12, 13]. The activation of glycolysis and glutaminolysis in cancer cells depends on two ubiquitin ligases, which control the transient appearance and metabolic activity of the glycolysis-promoting enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) and glutaminase 1 (GLS1), the first enzyme of glutaminolysis pathway [12].

Gliomas constitute one of the most aggressive groups of malignant neoplasms with poor survival prognosis and scarce therapeutic options. Aberrant vascularization, common in expanding solid tumors, results in deficiency of oxygen and nutrients. Glucose shortage associated with malignant progression triggers apoptosis through the endoplasmic reticulum unfolded protein response [14].
To some extent, a reduced glucose flux may be causative to endoplasmic reticulum stress [14]. Thus, a better understanding of effects of glucose and glutamine deprivations on genes expression especially in relation to endoplasmic reticulum stress is required to elaborate therapeutical strategies of cell sensibilization, based on the blockade of survival mechanisms [4, 14–18].

The endoplasmic reticulum is a key cellular compartment, extremely sensitive to perturbations of its homeostasis. Such perturbations, which affect the ER folding capacity, activate a set of signaling pathways, named the unfolded protein response. The latter plays an important role in metabolic integration [5, 6, 19]. In mammals this adaptive response is mediated by three membrane-spanning sensory proteins, among which IRE1 is the most evolutionary conserved and an indispensable [1, 6, 7, 11]. The IRE1 enzyme possesses two enzymatic activities: protein kinase and endoribonuclease. Recently it was demonstrated, that protein kinase of IRE1 is responsible not only for autophosphorylation but also indirectly controls expression of certain genes through phosphorylation of heterologous substrates [7, 20]. The IRE1 endoribonuclease performs a unique cytosolic splicing of the pre-XBP1 (X-box binding protein 1) mRNA whose mature transcript encodes a transcription factor, which stimulates the expression of numerous unfolded protein response specific genes, and also is involved in the degradation of a specific subset of mRNA and miRNA [21–26].

Tumor growth is tightly associated with the endoplasmic reticulum stress response signaling pathways, which are linked to the cell proliferation and death processes [2, 3, 8]. It is well known that \textit{IL13RA2} (interleukin 13 receptor, alpha 2), \textit{CD24} (signal transducer CD24 molecule), \textit{KRT18} (keratin 18), \textit{ING1} (inhibitor of growth family, member 1), \textit{ING2}, \textit{ENDOG} (endonuclease G) and many other genes play an important role in the regulation of numerous metabolic and proliferative processes as well as control of tumorigenesis [27–31]. The \textit{IL13RA2} gene is often overexpressed in glioma and other tumors [27]. CD24 encodes a sialoglycoprotein that modulates growth and differentiation signals [29]. The \textit{ING1} and \textit{ING2} genes encode tumor suppressor proteins that can induce cell growth arrest and apoptosis [30, 32]. Furthermore, the \textit{ING1} is a nuclear protein that physically interacts with the tumor suppressor protein TP53 and is a component of its signaling pathway. Reduced expression and rearrangement of this gene have been detected in various cancers [33, 34]. Moreover, \textit{ING1} protein stabilizes TP53 by inhibiting its polyubiquitination [35].

Recently was shown that \textit{KRT18} (keratin 18) also contributes to decreased malignancy of non-small cell lung carcinoma and is directly regulated by \textit{EGR1} (early growth response 1) [36]. There is data that the decreased expression of \textit{MYL9} (myosin, light chain 9, regulatory) may play an important role in tumor progression of prostate cancer [31]. It is possible that membrane trafficking proteins \textit{BET1} (Bet1 Golgi vesicular membrane trafficking protein) and \textit{BET3/TRAPP C3} (trafficking protein particle complex 3), which participate in vesicular transport from the endoplasmic reticulum to the Golgi complex, also involved in the endoplasmic reticulum stress responsible transport of unfolded proteins and tumorigenesis [37]. The \textit{ENDOG}, \textit{POLG} (DNA directed polymerase gamma), \textit{TSFM} (Ts mitochondrial translational elongation factor), and \textit{MTIF2} (mitochondrial translational initiation factor 2) genes encode mitochondrial proteins, which are related to the control of mitochondrial genome function as well as to cell proliferation [38–42]. Moreover, \textit{ENDOG} regulates an integral network of apoptotic endonucleases, which appear to act simultaneously before and after cell death by destroying the host cell DNA [38, 43].

The aim of this study was to investigate the effects of glucose and glutamine deprivation on the expression of a subset of genes encoding factors and enzymes (\textit{IL13RA2}, \textit{KRT18}, \textit{CD24}, \textit{ING1}, \textit{ING2}, \textit{MYL9}, \textit{BET1}, \textit{BET3/TRAPP C3}, \textit{ENDOG}, \textit{POLG}, \textit{TSFM}, and \textit{MTIF2}), which participate in the regulation of cell proliferation and apoptosis, in U87 glioma cell line and its subline with IRE1 loss of function [36]. There is data that the decreased expression especially in relation to endoplasmic reticulum polyubiquitination [35].

\textit{Experimental articles}

\textit{Materials and Methods}

\textit{Cell Lines and Culture Conditions}

The glioma cell line U87 (HTB-14) was obtained from ATCC (USA) and grown in high glucose (4.5 g/l) Dulbecco’s modified Eagle’s minimum essential medium (DMEM; Gibco, Invitrogen, USA) supplemented with glutamine (2 mM), 10% fetal bovine serum (Equitech-Bio, Inc., USA), penicillin (100 units/ml; Gibco,
USA) and streptomycin (0.1 mg/ml; Gibco) at 37 °C in a 5% CO2 incubator. Glucose and glutamine deprivation conditions were created by exchanging the complete DMEM medium in culture plates with DMEM medium lacking glucose or glutamine. Plates were exposed to these conditions for 16 h.

In this work we used two sublines of U87 glioma cells. One subline was obtained by selection of stable transfected clones with overexpression of vector (pcDNA3.1), which was used for creation of dominant-negative construct (dnIRE1). This untreated subline was used for creation of dominant-negative expression level of glutamine and glucose deprivations on the glioma cells) in the study of the effects of glioma cells was used as control (control glioma cells). One subline was obtained by selection of stable transfected clones with overexpression of dnIRE1 and has suppressed both protein kinase and endoribonuclease activities of this bifunctional signaling enzyme of endoplasmic reticulum stress [20]. Previously was shown that these cells have low proliferation rate and do not express XBP1 alternative splice variant, a key transcription factor in IRE1 signaling, after induction endoplasmic reticulum stress [20, 44]. The expression levels of these conditions for 16 h. glutamine deprivation conditions were created by culturing plates with DMEM medium lacking glucose or glutamine. Plates were exposed to these conditions for 16 h.

**RNA isolation**

Total RNA was extracted from glioma cells using Trizol reagent according to manufacturer protocols (Invitrogen, USA). The RNA pellets were washed with 75% ethanol and dissolved in nuclease-free water. For additional purification RNA samples were re-precipitated with 95% ethanol and re-dissolved again in nuclease-free water. RNA concentration and spectral characteristics were measured using NanoDrop Spectrophotometer ND1000 (PEQLAB, Biotechnologie GmbH).

**Reverse transcription and quantitative PCR analysis**

QuantiTect Reverse Transcription Kit (QIAGEN, Germany) was used for cDNA synthesis according to manufacturer protocol. The expression levels of E2F8, EPAS1, HOXC6, TBX3, Tbx2, GTF2F2, GTF2B, MAZ, SNAI2, TCF3, TCF8, and ACTB mRNA were measured in U87 glioma cells by real-time quantitative polymerase chain reaction (qPCR) using Mx 3000P QPCR (Stratagene, USA) and Absolute qPCR SYBRGreen Mix (Thermo Fisher Scientific, Abgene House, UK). Polymerase chain reaction was performed in triplicate using specific primers, which were received from Sigma-Aldrich (USA).

For amplification of IL13RA2 (interleukin 13 receptor, alpha 2) cDNA we used forward (5′-TCTGAGGACACCTGGCATAAGG-3′) and reverse (5′-TCTGATGCCCTCACAATAGGG-3′) primers. The nucleotide sequences of these primers correspond to sequences 591–610 and 742–723 of human IL13RA2 cDNA (NM_000640). The size of amplified fragment is 152 bp. The amplification of KRIT1 (keratin 18, type 1) cDNA was performed using two oligonucleotides primers: forward — 5′-CACAGTGTGAGTGGGA-3′ and reverse — 5′-GAGCTGCTCAGTGAGG-G-3′. The nucleotide sequences of these primers correspond to sequences 966–985 and 1129–1110 of human KRIT1 cDNA (NM_000224). The size of amplified fragment is 164 bp.

The amplification of CD24 (CD24 molecule; Signal transducer CD24) cDNA was performed using two oligonucleotides primers: forward — 5′-AACTAATGCCCACCAAGG-3′ and reverse — 5′-CTGTTTTCCTGTGACAT-3′. The nucleotide sequences of these primers correspond to sequences 590–609 and 777–758 of human CD24 cDNA (NM_013230). The size of amplified fragment is 169 bp. For amplification of MYL9 (myosin, light chain 9, regulatory), also known as MYBL2 (myosin regulatory light chain 2) cDNA we used forward (5′-ACCCACAGAAGAACTCT-3′) and reverse (5′-CCGTATACATTGCTCCATCTTT-3′) primers. The nucleotide sequences of these primers correspond to sequences 285–304 and 526–507 of human MYL9 cDNA (NM_006097). The size of amplified fragment is 242 bp.

For amplification of ING1 (inhibitor of growth family, member 1) cDNA we used forward (5′-CCAAGGGCAGTGTGATCTT-3′) and reverse (5′-CGGTATACATTGCTCCATCTTT-3′) primers. The nucleotide sequences of these primers correspond to sequences 1601–1620 and 1845–1826 of human ING1 cDNA (NM_005537). The size of amplified fragment is 245 bp. For amplification of ING2 (inhibitor of growth family, member 2) cDNA was performed using two oligonucleotides primers: forward — 5′-ACGTCTACACAGGCTTCC-3′ and reverse — 5′-TGCGGGGTCTTCTTGAAG-3′. The nucleotide sequences of these primers correspond to sequences 369–388 and 589–570...
of human ING2 cDNA (NM_001564). The size of amplified fragment is 221 bp.

For amplification of BET1 (Bet1 Golgi vesicular membrane trafficking protein), cDNA we used forward (5′-AGAAAGTTGCTTCTGCAGG-3′) and reverse (5′-AGTTCTCCATAGTTGCCAGGA-3′) primers. The nucleotide sequences of these primers correspond to sequences 49–68 and 333–314 of human BET1 cDNA (NM_005868). The size of amplified fragment is 166 bp.

The amplification of TRAPPC3 (trafficking protein particle complex 3), also known as BET3, cDNA was performed using two oligonucleotides primers: forward — 5′-GGCCCGAGGAAAGAGATGG-3′ and reverse — 5′-GATCTGGCCAATGATGCCTG-3′. The nucleotide sequences of these primers correspond to sequences 158–177 and 333–314 of human TRAPPC3 cDNA (NM_014408). The size of amplified fragment is 176 bp.

The amplification of ENDOG (endonuclease G) cDNA was performed using two oligonucleotides primers: forward — 5′-GGTCTACCTGAGCAAGTCG-3′ and reverse — 5′-CTGCCTGACTTT-3′. The nucleotide sequences of these primers correspond to sequences 659–678 and 843–824 of human ENDOG cDNA (NM_004435). The size of amplified fragment is 225 bp.

The amplification of TSFM (Ts Mitochondrial Translational Elongation Factor) cDNA was performed using two oligonucleotides primers: forward — 5′-GGACCTCGAAGAGATGG-3′ and reverse — 5′-AGGACTGTTGCGGTACAG-3′ primers. These primer nucleotide sequences correspond to 747–766 and 980–961 of human TSFM cDNA (NM_014408). The size of amplified fragment is 234 bp. The expression of beta-actin mRNA was used as control of analyzed RNA quantity.

Quantitative PCR analysis was performed using “Differential expression calculator” software. The values of IL13RA2, KRT18, CD24, ING1, ING2, MYRL2, BET1, TRAPPC3, ENDOG, POLG, TSFM, MTIF2, and ACTB gene expressions were normalized to the expression of beta-actin mRNA and represented as percent of control (100%). All values are expressed as mean ± SEM from triplicate measurements performed in 4 independent experiments. The amplified DNA fragments were also analyzed on a 2% agarose gel and visualized by SYBR* Safe DNA Gel Stain (Life Technologies, Carlsbad, CA, USA). Statistical analysis was performed according to Student’s test using Excel program as described previously [45]. All values are expressed as mean ± SEM from triplicate measurements performed in 4 independent experiments.

**Results and Discussion**

To test the effect of glutamine and glucose deprivations on expression levels of different genes, strongly related to both positive and negative control of cell proliferation in relation to IRE1 signaling enzyme function, we used the U87 glioma cell sublines, which constitutively express vector pcDNA3.1 (control cells) or dnIRE1 [10, 20]. Fig. 1 demonstrates that glutamine deprivation affects the expression of studied genes at mRNA level: up-regulates the expression of beta-actin (ACTB) (+30%), MYL9 (+13%), and MTIF2 (+18%) genes and down-regulates the expression of CD24 (−39%), ING2 (−35%), ENDOG (−36%), POLG (−24%), and TSFM (−18%) gene expressions as compared to control glioma cells growing with glutamine. It is interesting to note that more prominent changes in the expression levels were shown for CD24, ING2, and ENDOG genes as compared to other studied genes. At the same time, the expression of IL13RA2, KRT18, ING1, and BET3/TRAPPC3 genes at mRNA level was resistant to glutamine deprivation in control glioma cells.

We also analyzed the expression levels of genes encoded different proliferation
and apoptosis related factors and enzymes in glioma cells upon glucose deprivation. As shown in Fig. 2, glucose deprivation up-regulates the expression level of MYL9 (+55%) gene only and down-regulates of ING1 (–14%), ING2 (–20%), and MTIF2 (–13%) gene expressions in control glioma cells as compared to cells growing with glucose. More significant changes in the expression level of studied genes were shown for MYL9 gene only. At the same time, the expression of IL13RA2, KRT18, CD24, BET1, TRAPPC3, ENDOG, POLG, and TSFM genes at mRNA level was resistant to glucose deprivation in control glioma cells.

We next studied how inhibition of IRE1 modulates the effect of glutamine and glucose deprivation on the expression of IL13RA2, KRT18, CD24, ING1, ING2, MYL9, BET1, TRAPPC3, ENDOG, POLG, and TSFM, and MTIF2 genes. As shown in Fig. 3, the expression of IL13RA2, KRT18, CD24, MYL9, and POLG genes is resistant to glutamine deprivation condition in glioma cells with knockdown of signaling enzyme IRE1. However, the expression of genes encoding ING1, ING2, ENDOG, and POLG upon glutamine deprivation is significantly down-regulated in glioma cells with IRE1 knockdown: for ING1 in 2.4 fold, for ING2 in 2.0 fold, and for ENDOG (–16%). At the same time, the expression of four studied genes is up-regulated in U87 glioma cells upon this experimental condition (BET1, TRAPPC3, TSFM, and MTIF2): +60%, +23%, +26%, and +96%, respectively (Fig. 3). Therefore, inhibition of IRE1 completely abolishes the effect of glutamine deprivation on the expression CD24, MYL9, and POLG genes.

Results presented in Fig. 4 demonstrate that inhibition of signaling enzyme IRE1 leads to significant up-regulation of the expression of MTIF2 (+62%), MYL9 (+27%), IL13RA2 (+24%), BET1 (+23%), and TRAPPC3 (+19%) genes in glioma cells upon glucose deprivation condition. At the same time, the expression of four other genes is down-regulated in U87 glioma cells with IRE1 knockdown upon glucose deprivation: KRT18 (–13%), CD24 (–37%), ING1 (–48%), and ING2 (–27%). However, the expression of genes encoded ENDOG, TSFM, and POLG is resistant to glucose deprivation condition in glioma cells with IRE1 knockdown (Fig. 4).

Fig. 5 contains the results of comparative study of the sensitivity of IL13RA2, CD24, ING1, BET1, MTIF2, and BET3 (TRAPPC3) gene expressions to glutamine deprivation in two types of glioma cells: control cells and cells without IRE1 signaling enzyme function. It was shown that inhibition of IRE1 signaling enzyme enhances the sensitivity of IL13RA2, CD24, ING1, BET1, TRAPPC3, and MTIF2 genes expression to glutamine deprivation condition in glioma cells. At the same time, the sensitivity of MYL9 gene expression is eliminated upon glucose deprivation. As shown in Fig. 6, the sensitivity of ENDOG and POLG
genes expression to glutamine deprivation condition is significantly decreased upon inhibition of IRE1 enzyme function. At the same time, inhibition of IRE1 signaling enzyme significantly enhances the sensitivity of TSFM and MTIF genes expression in glioma cells to glutamine deprivation condition (Fig. 6).

We have also investigated the effect of inhibition of IRE1 signaling enzyme on sensitivity of IL13RA2, CD24, ING1, ING2, MYL9, BET1, TRAPPC3, ENDOG, POLG, TSFM, and MTIF2 genes expression in glioma cells to glucose deprivation condition (Fig. 6).

Fig. 7, the sensitivity of IL13RA2, CD24, ING1, BET1, and MTIF2 genes expression to glucose deprivation condition is significantly increased by inhibition of IRE1 enzyme function, but the sensitivity of MYL9 gene expression is decreased. Furthermore, inhibition of IRE1 signaling enzyme does not change the effect of glutamine deprivation on the expression IL13RA2 gene (Fig. 1 and 3) and the effect of glucose deprivation on the expression KRT18, ENDOG, and POLG genes (Fig. 2 and 4) in glioma cells.
Results of this study clearly demonstrated that the expression levels of almost all studied genes encoding proliferation-related factors and enzymes are affected by glutamine and glucose deprivation and inhibition of IRE1 modified sensitivity of these gene expressions to both glutamine and glucose deprivations. Our results are consistent with data that glycolysis and glutaminolysis are related to the control of cell proliferation through regulation of cell cycle and tumor suppressor genes [12, 46, 47]. Recently, we have shown that genes encoded insulin-like growth factor binding proteins are strongly dependent on the endoplasmic reticulum stress and particularly on its IRE1 signaling pathway, because inhibition of IRE1, especially its endoribonuclease activity, significantly affects expression of these genes, and that inhibition of IRE1 modifies sensitivity of insulin-like growth factor binding protein genes expression to glucose deprivation [48, 49].
In this study we have shown that glutamine deprivation down-regulates the expression level of an anti-proliferative CD24 gene and that inhibition of IRE1 signaling enzyme function in U87 glioma cells eliminates this effect and that these results correlate with a suppression of cell proliferation by IRE1 inhibition [10]. At the same time, the expression level of this gene is resistant to glucose deprivation in control glioma cells, but inhibition of IRE1 introduces sensitivity of CD24 gene expression to glucose deprivation. Thus, our results argue with data from Colombo et al. [12], who show that glucose and glutamine are required for tumor progression through cell cycle control and that deprivation of these substrates of glycolysis and glutaminolysis have opposite effect. Moreover, effects of glucose and glutamine deprivation conditions on the expression of genes studied in this work are gene-specific and are similar for ING2 and MYL9 genes and different for many other genes (CD24, ING1, BET1, ENDOG, POLG, TSFM, and MTIF2).
In general, our results are consistent with data that glycolysis and glutaminolysis are related to the control of cell proliferation through regulation of genes controlling cell proliferation and tumor suppressor genes. Inhibition of IRE1, a central mediator of endoplasmic reticulum stress response, preferentially modified sensitivity of these genes to glutamine and glucose deprivations and possibly contributes to slower glioma growth. However, molecular mechanisms of the regulation of these genes by glutamine and glucose deprivation through the endoplasmic reticulum stress response pathways are complex and warrant further investigation for clarification of the role of endoplasmic reticulum stress in metabolic disease.

Results of this study clearly demonstrated that the expression levels of almost all studied genes (IL18RA2, KRT18, CD24, ING1, ING2, MYL9, BET1, TRAPPC3, ENDOG, POLG, TSPM and MTIF2), which encode key factors and enzymes responsible for control of cell proliferation and apoptosis, are affected by glucose and glutamine deprivations in glioma cells in gene-specific manner and the sensitivity of their expression levels to the deficiency of essential nutrients is modified by IRE1 signaling branch of endoplasmic reticulum stress.

REFERENCES


ПРИГНІЧЕННЯ ЗАЛЕЖНОГО ВІД ІНОЗИТОЛА ЕНЗИМУ-1 ЗМІНЮЄ ВПЛИВ ДЕФІЦІТУ ГЛЮКОЗИ ТА ГЛУТАМИНУ НА РІВЕНЬ ЕКСПРЕСІЇ БІЛЬШОСТІ ГЕНІВ, ЩО КОНТРОЛОЮЮТЬ ПРОЦЕСИ ПРОЛІФЕРАЦІЇ, У КЛІТИНАХ ГЛІОМИ ЛІНИЇ U87

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Метою роботи було вивчення експресії генів, що кодують фактори та ензими, які стосуються проліферації, зокрема IL13RA2, KRT18, CD24, ING1, ING2, MYL9, BET1, TRAPPC3, ENDOG, POLG, TSFM та MTIF2, у клітинах глиоми лінії U87 за умов дефіциту глюкози та глутаміну залежно від пригнічення IRE1 — центрального медіатора стресу ендоплазматичного ретикулуму. Встановлено, що за умов дефіциту глутаміну спостерігається посилення експресії генів BET1, MYL9 та MTIF2 і зниження експресії генів CD24, ING2, ENDOG, POLG та TSFM у контрольних клітинах глиоми (з нативним IRE1). Водночас за умов дефіциту глюкози зростає рівень експресії гена MYL9 і зменшується рівень генів ING1, ING2 та MTIF у контрольних клітинах глиоми. Таким чином, ефект дефіциту глутаміну залежить від рівня експресії гена MYL9 і зменшується рівень генів ING1, ING2 та MTIF у контрольних клітинах глиоми (з нативним IRE1). Водночас за умов дефіциту глутаміну залежно від функції IRE1 і, можливо, зумовлює зниження інтенсивності росту пухлин після пригнічення цього ензиму.

Ключові слова: експресія генів, пов’язаних з проліферацією, пригнічення IRE1, дефіцит глюкози та глутаміну, клітини глиоми.

УГНЕТЕНИЕ ЗАВИСИМОГО ОТ ИНОЗИТОЛА ЭНЗИМА-1 ИЗМЕНЯЕТ ВЛИЯНИЕ ДЕФИЦИТА ГЛЮКОЗИ И ГЛУТАМИНА НА УРОВЕНЬ ЭКСПРЕССИИ БОЛЬШИНСТВА ГЕНЫ, КОТОРЫЕ КОНТРОЛИРУЮТ ПРОЦЕССЫ ПРОЛІФЕРАЦИИ В КЛЕТКАХ ГЛІОМЫ ЛІНИЇ U87

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Целью работы было изучение экспрессии генов, кодирующих факторы и энзимы, имеющие отношение к пролиферации, в частности IL13RA2, KRT18, CD24, ING1, ING2, MYL9, BET1, TRAPPC3, ENDOG, POLG, TSFM и MTIF2, в клетках глиомы линии U87 при дефиците глюкозы и глутамине в зависимости от угнетения ИРЕ1 — центрального медиатора стресса эндоплазматического ретикулума. Установлено, что при дефиците глутамина отмечается усиление экспрессии генов BET1, MYL9 и MTIF2 в клетках глиомы линии U87 при нативном ИРЕ1. В то же время при дефиците глюкозы происходит увеличение уровня экспрессии гена MYL9 и снижается экспрессия генов ING1, ING2 и MTIF в клетках глиомы линии U87. Таким образом, эффект дефицита глутамина и глюкозы на экспрессию генов в клетках глиомы в зависимости от функции ИРЕ1 является геноспецифическим. Угнетение ИРЕ1 с помощью dnIRE1 существенно изменяет влияние дефицита глутамин в клетках глиомы и глутамину на экспрессию большинства исследованных генов, но по-разному по направлению и величине, особенно для генов ING2, CD24 и MTIF. Продемонстрировано, что экспрессия генов, имеющих отношение к пролиферации, изменяется при дефиците глутамин и глюкоза в зависимости от функции ИРЕ1 и, возможно, обусловливает в снижение интенсивности роста опухолей после угнетения ИРЕ1.

Ключевые слова: экспрессия генов, связанных с пролиферацией, угнетение ИРЕ1, дефицит глутамин и глутамин, клетки глиомы.