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MOLECULAR MECHANISMS OF DRUG RESISTANCE OF GLIOBLASTOMA Part 1: ABC FAMILY PROTEINS AND INHIBITORS

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The most common high-grade brain tumor in the adult population is glioblastoma. The life expectancy of patients with this tumor does not exceed 12-15 months, while relapses are observed in 100% of cases. One of the main reasons for the low efficiency of glioblastoma therapy is its multidrug resistance. In the development of the latter, transporter proteins of the ABC family play a key role. In this part, the emphasis is on the search for new molecular targets among growth factors, their receptors, signal transduction kinases, microRNAs, transcription factors, protooncogenes, and tumor suppressor genes involved in the regulation of proteins and genes of the ABC family and associated with the development of multidrug resistance in glioblastoma cells. The review also discusses the mechanisms of the cytotoxic action of inhibitors: ABC family proteins, tyrosine kinase receptors, non-receptor tyrosine kinases, vascular endothelial growth factor, kinases of signaling cascades, transcription factors, histone deacetylases, methyltransferases, replication and synthesis of DNA, microtubules and proteasome used in glioblastoma therapy or undergoing clinical trials.

Keywords: glioblastoma; multidrug resistance; chemotherapy drugs; inhibitors; ABC-family transporter proteins; growth factors and receptors; signal transduction kinases; microRNA; transcription factors.

МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТИ ГЛИОБЛАСТОМЫ Часть 1. БЕЛКИ ABC-СЕМЕЙСТВА И ИНГИБИТОРЫ

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Наиболее часто встречаемой высокозлокачественной опухолью головного мозга у взрослого населения является глиобластома. Продолжительность жизни пациентов с данной опухолью не превышает 12–15 мес., при этом в 100 % случаев наблюдаются рецидивы. Одна из главных причин невысокой эффективности терапии глиобластомы — ее множественная лекарственная устойчивость. В развитии последней ключевую роль играют белки-транспортеры ABC-семейства. В данной части акцент сделан на поиске новых молекулярных мишеней среди ростовых факторов, их рецепторов, киназ сигнальной трансдукции, микроРНК, транскрипционных факторов, протоонкогенов и генов-супрессоров опухолей, участвующих в регуляции белков и генов ABC-семейства и связанных с развитием множественной лекарственной устойчивости в клетках глиобластомы. В обзоре также приведены механизмы цитотоксического действия ингибиторов (белки ABC-семейства, тирозинкиназные рецепторы, нерецепторные тирозинкиназы, факторы роста эндотелия сосудов, киназы сигнальных каскадов, транскрипционные факторы, гистоновые деацетилазы, метилтрансферазы, топоизомеразы, репликация и синтез ДНК, микротрубочек и протеасом), применяемые при терапии глиобластомы или находящиеся на стадии клинических испытаний.

Ключевые слова: глиобластома; множественная лекарственная устойчивость; химиопрепараты; ингибиторы; белки-транспортеры ABC-семейства; ростовые факторы и рецепторы; киназы сигнальной трансдукции; микроРНК; транскрипционные факторы.

List of abbreviations

GBM, glioblastoma; BBB, blood–brain barrier; MDR, multidrug resistance; TMZ, temozolomide; ABCB1, ATP-binding cassette protein-1 subfamily B; ABCC1, ATP-binding cassette protein-1 subfamily C; BCRP, breast cancer resistance protein; EGFR, epidermal growth factor receptor; HDAC, histone deacetylases; MAPK, mitogen-activated protein kinase; MELK, maternal embryonic leucine zipper kinase; NF-κB, nuclear factor kappa B; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; P-gp, P-glycoprotein; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Glioblastoma (GBM) is the most common type of high-grade brain tumor in the adult population. It accounts for 77%–81% of all malignant primary brain tumors, and its incidence reaches 10 people per 100,000 [1]. The tumor can occur at any age but is especially common at 45–75 years [1]. The five-year overall survival rate of patients with GBM at the age of 20–44 years is 13%, and at the age of 55–64 years, it is only 1% [2]. The standard treatment protocol for GBM includes surgical resection of the tumor, followed by radiotherapy and chemotherapy [3]. With this treatment regimen, the life expectancy of patients is only 14.6 months, with 100% relapse [4].

Because of the deregulation of several physiological and pathological molecular, genetic, subcellular, and cellular mechanisms, the GBM cells become radio- and chemoresistance, which makes the therapy less effective. The key participants in the previously mentioned mechanisms are growth factors, cytokines and their receptors, proteins of signal transduction cascades, transcription factors, miRNAs, oncogenes, and tumor suppressor genes. All the external influences on the tumor cells are integrated using signaling cascades, transcription factors, miRNAs, and genes. Therefore, a detailed study on the molecular mechanisms in GBM cells will identify new key targets and nodes that can be used as markers of effective targeted therapy.

This review highlights the molecular mechanisms of GBM multidrug resistance (MDR) in pathophysiological cellular processes, with a focus on the transporter proteins of the ATP-binding cassette (ABC) family and the use of inhibitors in the treatment of GBM.

Drug resistance and the ABC family transporter proteins

The overexpression of ABC transporters plays a key role in the development of MDR in tumor cells, including GBM. In humans, 49 genes encoding ABC proteins were identified, which are divided into seven subfamilies: ABC1 (ABCA), MDR/TAP (ABCB), MRP (ABCC), ALD (ABCD), OABP (ABCE), GCN20 (ABCF), and white (ABCG) [5].

The ABCA subfamily includes 13 proteins, of which ABCA1, ABCG1, and ABCG4 are involved in excreting cholesterol and phospholipids from the cells [6].

Simultaneously, genes and proteins belonging to the subfamilies ABCB, ABCC, and ABCG are most often overexpressed in GBM. The structure of these proteins is well characterized [7], but the exact mechanisms of their regulation and protein and gene targets are underinvestigated.

ABCB1

Of the eleven ABCB proteins, protein-1 (ABCB1; P-glycoprotein; P-gp; Mdr1; CD243) is the most studied. This transmembrane protein, consisting of two ATP-binding and two transmembrane domains, is expressed on the apical membrane of the capillary endothelial cells forming the blood–brain barrier (BBB) and in the U87 human glioma stem cells [8]. The ABCB1 protein is involved in excreting the anticancer drugs (etoposide, doxorubicin, vinblastine, gefitinib, sunitinib, tacrolimus, and temozolomide), organic cations, carbohydrates, oligosaccharides, lipids, steroids, bilirubin, amino acids, peptides, antibiotics, xenobiotics, dexamethasone, and cardiac glycosides (digoxin) from cells [9, 10]. P-gp expression was found on the nuclear membrane of the cells [11]. However, the physiological significance of the previously mentioned phenomenon has not yet been established. The variety of ABCB1 substrates predetermines the variety of functions such as regulation of the bioavailability and distribution of chemotherapy drugs and restriction of their transfer through the BBB to the brain and the protection of tumor stem cells from toxins. Overexpression of ABCB1 in the intestinal enterocytes slows down the penetration of chemotherapy drugs into the bloodstream, which prevents them from reaching therapeutic concentrations in patients with GBM [12].

ABCB1 gene expression and activity are regulated by transcription factors, signal transduction kinases, miRNAs, and growth factors. For example, many transcription factors bind to the *ABCB1* gene promoter, namely, protein p53, tyrosine domain containing protein-1 (YB-1), nuclear factor-κB (NF-κB), protein-containing cAMP binding element (CREB), transcription factor-1 containing a lysine domain and MADS domains (AP-1), and an enhancer of the subunit of the zeste 2 polycomb repressive complex 2 (EZH2) [12–14].

Simultaneously, in GBM, the previously mentioned transcription factors are activated by signaling cascades with the participation of phosphatidylinositol-3-kinase/protein kinase-B, the mechanistic target of rapamycin kinase (Pi3k/Akt/

mTOR), Wnt5a-Frizzled, the receptor/kinase-3β-glycogen synthase (Wnt5a/Frizzled/Gsk-3β), Ras/Raf/mitogen-activated protein kinase (MAPK), and c-Jun/c-Jun N terminal kinase (JNK) [15–17]. Activation of the Pi3k/Akt/NF-κB cascade increases the expression of O-6-methylguanine-DNA-methyltransferase (MGMT) and; hence, the resistance of GBM cells to the main chemotherapy drug, temozolomide (TMZ) [18]. Therefore, upon activation of this pathway, the expression of the *ABCB1* gene will increase the resistance of GBM to TMZ. More detailed studies have shown that the MAPK/Erk1/2 and p38MAPK cascades stimulate P-gp, and c-Jun/JNK inhibits *ABCB1* expression (Figure) [19, 20]. In turn, p38MAPK is activated by CD133 membrane glycoprotein, which colocalizes on GBM membranes with the epidermal growth factor receptor (EGFR) [21]. The latter triggers the signal transducer and transcription activator 3 (STAT3) cascade, which also enhances tumor progression [22]. It is suggested that *ABCB1* expression may be inhibited by the transcription factor O3A containing a forkhead domain (FOXO3a) since it is activated by PTEN- (deleted phosphatase and tensin homolog on chromosome 10) mediated inhibition of the Pi3k/Akt cascade [23].

MicroRNAs are also involved in the regulation of *ABCB1* gene transcription [24, 25]. For example, has-miR-4261 inhibits P-gp expression through MGMT suppression, which increases cell sensitivity to TMZ [24]. MiR-200c also suppresses P-gp expression through the JNK2/c-Jun signaling pathway [26]. MiR-130a possibly activates *ABCB1* through the Pi3k/Akt/PTEN/mTOR and Wnt/β-catenin signaling cascades (Figure) [25].

The level of long noncoding RNA SNHG15 correlates with high levels of β-catenin, EGFR, transcription factor-2 containing the SRY domain (SOX-2), and cell division kinase-6 (CDK6) in TMZ-resistant GBM cells. SNHG15 enhances

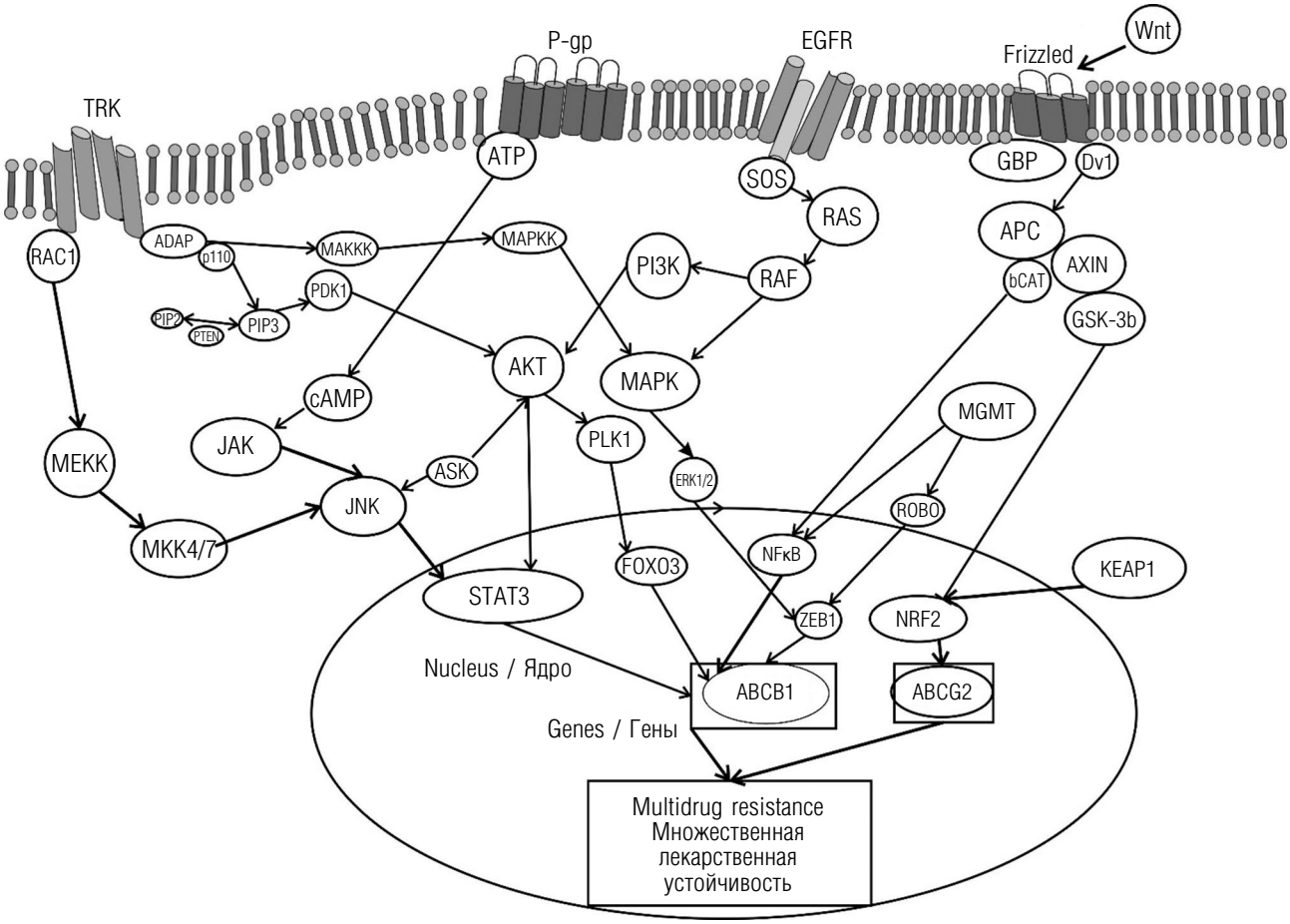

Figure. Intracellular mechanisms of multidrug resistance of glioblastoma involving genes *ABCB1* and *ABCG2*. See text for explanations

Рисунок. Внутриклеточные механизмы множественной лекарственной устойчивости глиобластомы с участием генов *ABCB1* и *ABCG2*. Объяснения см. в тексте

tumor progression by inhibiting the miR-627-5p suppressor, leading to the activation of CDK6 and SOX-2 [27].

ABCB1 expression is regulated at the posttranscriptional level by degradation and intracellular redistribution of P-gp. For example, serine-threonine kinase PIM-1 prevents P-gp ubiquitination and its degradation by proteasome proteins [28]. In another case, the small GTPase of the RAS family RAB5 suppresses P-gp endocytosis and increases the number of its molecules on the cell membrane, while RAB4 activates endocytosis and reduces the number of molecules on the membrane [29]. In GBM, the *ABCB1* promoter is methylated [30].

The activation of suppressor genes for amiloride-sensitive cation channels 3 and 4 (*ACCN3* and *ACCN4*) suppresses EGFR expression and, through it *ABCB1* activity [31]. In GBM U251 cells, the P-gp expression is suppressed by inhibiting Bcl-2 when exposed to bone morphogenetic protein-4 (BMP4) [32].

ABCB1 expression in GBM cells is activated in cyclic hypoxia due to exposure to hypoxia-inducible factor-1α (HIF-1α), which reduces the sensitivity of tumor cells to doxorubicin [33]. In turn, HIF-1α stimulates the synthesis of carboxylic anhydrase-9 (CA9) in GBM cells under hypoxic conditions, which further reduces the pH of the tumor microenvironment, enhancing its resistance to chemotherapy [34]. Therefore, *CA9* expression is expected to be positively correlated with the activity of the P-gp protein. HIF-1α also activates the expression of erythroid-like nuclear transcription factor-2 (NRF2), which enhances the resistance of GBM to chemo- and radiotherapy [35]. In this regard, NRF2 expression can correlate with the activity of *ABCB1* and P-gp. On the contrary, in aerobic glycolysis, CDC-like kinase-1 (CLK1) enhances glucose utilization and suppression of lactate formation in GL261 glioma cells. When CLK1 is activated through the AMP-activated protein kinase (AMPK)/mTOR signaling cascade, HIF-1α expression is inhibited [36]. CLK1 can be considered a new target of action aimed at *ABCB1* and P-gp.

Currently, suppressing *ABCB1* expression and P-gp activity is the mechanism of action of many drugs, such as amiodarone, azithromycin, captopril, clarithromycin, cyclosporine, piperine, quercetin, quinidine, quinine, reserpine, ritonavir, tariquidar, and verapamil.

ABCC

Expression of ABCC proteins (MRP) including the subfamilies MRP1 (ABCC1; multidrug resistance protein 1), MRP3 (ABCC3), MRP4 (ABCC4), and MRP5 (ABCC5) is also observed in GBM cells [37]. ABCC1 is expressed in the tumor stem cells and is weakly expressed in adherent GBM cells [38]. ABCC1 removes chemotherapy drugs (vincristine, etoposide, doxorubicin, methotrexate, cisplatin, and mitoxantrone), C4 leukotriene, conjugates of estrogen, glucuronides, sulfate conjugates of steroid hormones, heavy metals, organic amines, and lipids from the tumor cells [39]. Proteins MRP3 and MRP4 are involved in excreting glucocorticoids and prostaglandins E_1 and E_2, respectively, and MRP5 is involved in excreting chemotherapy drugs (thiopurine, 6-mercaptopurine, and thioguanine) and their conjugates with glutathione and glucosyl- and sulfatidylsteroids [40]. The proteins ABCC4 and ABCC5 regulate intracellular signaling to the nucleus through cyclic adenosine monophosphate (cAMP). Additionally, ABCC5 promotes the degradation of phosphodiesterases and the elimination of cyclic nucleotides [41]. Proteins ABCC8 and ABCC9, being sulfonylurea receptors, form ATP-binding subunits of the potassium channel and inhibit the activity of GBM cells [42]. All these proteins can be considered new targets for targeted anticancer drugs.

Many mechanisms are used to regulate *ABCC* genes. For example, the expression of *ABCC2* and *ABCC4* is suppressed by the action of secreted frizzled-like protein-4 (sFRP4) and tacrolimus and the expression of *ABCC1* in stem and GBM cells [43]. Activation of *ABCC1* and *ABCC3* is stimulated by MGMT through the insulin-like growth factor 1 (IGF1R) and Pi3k/Akt/MYC cascade and the transcription factor EZH2, respectively; therefore, MRP1 and MRP3 proteins may be involved in the development of GBM resistance to TMZ [44].

The large vaulted ABCC subfamily protein (MVP/LRP) is activated through the EGFR and SHH/GLI signaling cascade but is inhibited by the maternal embryonic leucine zipper domain containing kinase (MELK) and PTEN [45]. In turn, EGFR activation in GBM enhances the expression of the *c-MET* receptor for hepatocyte growth factor (HGF) [46]. *c-MET* and HGF can activate the expression of *ABCC* and *ABCB1*. Additionally, the translation of *c-MET* and PTEN

is regulated by Musashi RNA binding proteins 1 and 2 (MSI1; MSI2) [47]. For this reason, MSI1 and MSI2 may be involved in the regulation of *ABCC* genes. Another study examined the effect of the hedgehog (HH) pathway on the sensitivity of glioma cells to vincristine, depending on the *MRP1* gene expression. The inhibition of the HH cascade through suppression of the *MRP1* gene enhances the chemotherapy drug cytotoxicity [48]. This indicates the involvement of the HH cascade in the regulation of MDR genes in gliomas. An interesting study investigated the expression of ABCA1, MRP4, and MRP5 in GBM stem cells during differentiation and suggested that differentiation enhances MDR in GBM cells. This hypothesis was confirmed by detecting overexpression of ABC transporters in differentiated GBM cells compared with stem cells [49, 50].

ABCE

Of the ABCE subfamily, ABCE1, an inhibitor of ribonuclease L, may be involved in the development of MDR. This enzyme binds to 5'-phosphorylated 2',5'-linked oligoadenylates and inhibits the 2-5L A/RNA signaling pathway. The ABCE1 protein, together with eukaryotic translation initiation factors (eIF2, eIF5, and eIF3), purifies the 40S subunits of ribosomes, participating in their biosynthesis and transport from the nucleus [51]. Thus, ABCE1 promotes protein biosynthesis and the development of MDR.

ABCG2

GBM tumors and stem cells often overexpress the *ABCG2* gene and breast cancer resistance protein (BCRP), which is involved in the development of tumor resistance to chemotherapy drugs [52]. BCRP is found on the nuclear membrane of LN229 GBM cells, the significance of which is still unclear [14]. It is suggested that *ABCG2* overexpression is the result of gene rearrangement or amplification, increasing the resistance of GBM to mitoxantrone, topotecan, irinotecan, epirubicin, camptothecin, daunorubicin, doxorubicin, and anthracyclines [53, 54]. *ABCG2* expression is inhibited by sFRP4 and LRIG1 through their suppression of EGFR expression and activation of the eukaryotic translation initiation factor 2 alpha kinase-3 (PERK)/activation transcription factor-4 (ATF4) cascade [31, 43]. Expression of the *ABCG2* gene is also inhibited by miR-145 and activated by the transcription factors NRF2 and EZH2 (Figure) [55, 56].

Coexpression of P-gp and BCRP is observed in GBM cells and BBB epithelial cells due to their joint functioning [57]. A correlation has been established between the expression of BCRP proteins and tyrosine kinase receptor-1 with immunoglobulin-like and EGF-like domains (Tie), confirming the association of BCRP with angiogenesis [58]. The suppression of BCRP activity underlies the mechanism of action of many drugs (vinblastine, vincristine, temozolomide, topotecan, irinotecan, mitoxantrone, camptothecins, anthracyclines, elacridar, and celecoxib) [31, 59, 60].

Drug resistance inhibitors in glioblastoma

Many chemotherapy drugs or targeted therapies are used (or studied in clinical trials) to treat GBM. Most of them are inhibitors. According to their mechanism of action, they can be divided into the following: inhibitors of ABC transporters, heat shock proteins, tyrosine kinase receptors, signaling cascade kinases, enzymes, microtubules, proteasomes, transcription factors, and DNA synthesis (Table).

Table / Таблица

Clinical trials of targeted drugs for glioblastoma therapy
Клинические испытания таргетных препаратов для терапии глиобластомы

Drug	Target	Trial phase	Reference
AEE788	VEGFR, EGFR	I	61
Aflibercept	VEGF-A, VEGF-B, PLGF	I	62
Bevacizumab	VEGF	BEV + IR, III	63, 64
Vandetanib	VEGFR2, EGFR	I	65
Vatalanib (PTK787)	VEGFR1-3, PDGFRβ, c-kit TKI	I	66
Gefitinib	EGFR	II	67
Golvatinib (E7050)	MET/HGF	I	68

End of Table / Окончание таблицы

Drug	Target	Trial phase	Reference
Depatuxizumab (ABT-414, ABT-806)	EGFR	II	69
Cabozantinib (XL-184)	VEGFR2, *c-MET* TM3 + radiotherapy	II	70
Lapatinib	EGFR, HER-2	II	71
Lenvatinib (E7080)	VEGFR2, VEGFR3, FGFR1, c-kit, PDGFRβ	*In vivo*	72
Nimotuzumab	nimotuzumab EGFR antibodies in combination with TMZ	III	73
Olaratumab (IMC-3G3)	PDGFRα	II	74
Onartuzumab (MetMAb)	MET/HGF	II	75, 76
Pazopanib (GW786034)	VEGFR1-3, PDGFRα, PDGFRβ, c-Kit TKI	II	77
Panitumumab (ABX–EGF)	EGFR	II	78
Pertuzumab	HER2	FDA approved	79
Ramucirumab (IMC-1121B)	VEGFR2	II	80
Rilotumumab (AMG 102)	MET/HGF	II	81
Rindopepimuth (CDX-110)	EGFRvIII	III	82
Sorafenib	VEGFR2, Raf1, PDGFR, c-Kit, Flt3	I	83
Sunitinib	VEGR2, PDGFRα, PDGFRβ, c-Kit, Flt3	II	84
Tacrolimus (FK506)	FK506-binding protein 12 (FKBP12)	*In vitro*	85
Temsirolimus	mTOR	I/II	86
Tivantinib (ARQ197)	MET	*In vitro*, U251, T98MG, I	87
Tivozanib	VEGR3	II	88
Trastuzumab	HER2	*In vivo*	89
Ficlatuzumab (AV-299)	MET/HGF	I	90
Cediranib	VEGFR1-3, PDGFRβ, c-kit	II	91
Cetuximab (C225)	EGFR	I	92
Cilengitide	Integrins αvβ3 αvβ5	II/III	93
Everolimus	mTOR	I/II	94, 95
Enzastaurin (LY317615)	PKCβ, Pi3k/Akt/mTOR	III	96
Erlotinib (OSI-774)	EGFR	II	97
Zetakin	IL13Rα2	I	98
^{125}I-MAb	EGFR	II	99
INCB28060 (INC280, capmatinib)	MET/HGF	Ib/II	100
mAb 806 (ABT-806)	ΔEGFR	I	101
MK0752	γ-Secretase	I	102
RO5323441	PLGF	I	103
Tf-CRM107	Transferrin	I	104
scFvM58-sTRAIL	MRP3, TRAIL-R1, TRAIL-R2	MRP3	105
XL765 (SAR245409, voxtalisib)	PI3K/mTOR	*In vitro*, *in vivo*	106

N o t e: GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; FGFR1, fibroblast growth factor receptor; mTOR, mechanistic target of rapamycin kinase; PKCβ, protein kinase Cβ; PLGF, placental growth factor; TMZ, temozolomide.

ABC transporter inhibitors

In clinical practice, drugs suppressing the expression of P-gp and BCRP are used or studied in a phase of clinical trials. These include sunitinib malate (SU11248), an inhibitor of platelet-derived growth factor tyrosine kinase receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR), which inhibits the activity of P-gp and BCRP proteins through ATP hydrolysis [107]. Imatinib inhibits these proteins and PDGFR by suppressing the activity of cytochrome P4503A (CYP3A) [108]. However, imatinib enters nerve cells through the P-gp and BCRP transporters; therefore, the penetration of the drug into cells overexpressing these proteins is significantly restricted. With an increase in the concentration (0.5–50.0 μM) of imatinib, its accumulation in C6 glioma cells proportionally increases [109]. Other inhibitors of P-gp and BCRP include elacridar and pantoprazole, which increase the permeability of GBM cells to imatinib in mice by 1.8-fold and 4.2-fold, respectively [110].

Moreover, statins can be used as inhibitors of ABC transporters, since they stimulate the synthesis of nitric oxide and; therefore, participate in the tyrosine nitration of ABC transporters, reducing their activity [111].

Other P-gp inhibitors include verapamil and cyclosporin A, which inhibit calcium channels [112]. The following drugs are at the clinical trial phase: phosphodiesterase-5 inhibitors fumitremrergin, indolyl diketopiperazine, and Ko143 [(3S,6S,12aS)-1,2,3,4,6,7,12,12a-octahydro-9-methoxy-6-(2 methylpropyl)-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propionic acid 1,1-dimethylethyl ether], which inhibit ABCG2 [113].

A study by Spanish scientists showed that melatonin, a hormone of the pineal gland, stimulates promoter methylation by suppressing the expression of the *ABCG2* gene and BCRP protein, thereby synergistically enhancing the effect of TMZ on A172 human GBM cells [113]. Additionally, proteins containing methyl CpG binding domains (MBD2 and MeCP2) can methylate the *ABCG2* gene [114]. The activity of the *ABCG2* gene also decreases upon histone acetylation [115].

Tyrosine kinase receptor inhibitors

In GBM, EGFR and EGFRvIII are overexpressed, and therefore, their inhibitors (monoclonal antibodies and small molecules) are used for treatment. The monoclonal antibodies group includes cetuximab and panitumumab, while the small molecules group includes gefitinib, erlotinib, and lapatinib (Table) [66, 67]. Erlotinib inhibits the proliferation of stem cells and GBM cells, where *EGFR* gene amplification or EGFR overexpression is noted [97]. In patients with GBM, who experienced *EGFR* amplification but not EGFRvIII expression, the use of cetuximab increased progression-free survival and overall survival rates to 3.03 and 5.57 months, respectively, compared with 1.63 and 3.97 months in the group that was not using the drug [116].

Nonreceptor tyrosine kinase inhibitors

In GBM, overexpression of nonreceptor tyrosine kinase proto-oncogenes 1 and 2 (c-Abl, Arg) is often noted, which enhances tumor progression. Imatinib inhibits the expression of ABL1 and ABL2 kinases through the STAT3/HSP27/AKT/NF-κB signaling cascade and the expression of NF-κB target genes, induction of apoptosis, and cessation of cells in the G_2/M phase [117].

Vascular endothelial growth factor inhibitors

The monoclonal antibody bevacizumab is a VEGF inhibitor widely used in clinical practice. Its efficiency in treating GBM was confirmed in a sample of 637 patients who had an increase in progression-free survival rates (10.7 months) compared with the placebo group (7.3 months) [118]. A phase II clinical trial was conducted in 22 centers in Germany on 182 patients with GBM. The patients were distributed randomly into two groups and received bevacizumab and irinotecan with radiotherapy or daily TMZ. The trial showed an increase in the six-month progression-free survival rate ($p < 0.001$) to 79.3% in the group receiving bevacizumab and irinotecan with radiotherapy compared with the group receiving TMZ (42.6%). In absolute terms, the progression-free survival rate was increased from 5.99 to 9.7 months ($p < 0.001$). However, the overall survival rate did not change and amounted to 16.6 months in the group receiving bevacizumab and irinotecan with radiotherapy and 17.5 months in the group receiving TMZ [63].

Kinase signaling cascade inhibitors

Pi3k/mTOR inhibitors XL765 (SAR245409, voxtalizib), temsirolimus, and tacrolimus (target FKBP12; Table) are currently under clinical trials [85, 86]. Voxtalizib reduces the lactate/pyruvate

ratio in U87MG GBM cells, resulting in the inhibition of glycolysis, acidosis, and hypoxia [119]. Tacrolimus forms a complex with the FKBP12 protein, which suppresses the formation of calcineurin and the expression of ABCC1 in T98G cells, increasing their sensitivity to vincristine, etoposide, and taxol [120].

Transcription factor inhibitors

American researchers from Duke University revealed a synergistic cytotoxic effect of JSI-124 inhibitors (STAT3 target) and gefitinib on GBM cells. They increase the sensitivity of glioma cells to TMZ, 1,3-bis(2-chloroethyl) nitrosourea, and cisplatin [121]. Another STAT3 inhibitor, STX-0119, suppresses the expression of mTOR, S6, and protein-1 binding translation initiation factor 4E (4E-BP1) through the regulation of the expression of CHI3L1 chitinase-3-like protein-1 (YKL-40) in U87 GBM cells [122].

Inhibitors BAY117082, parthenolide, and MG132 (targeting NF-κB) have a fundamentally different mechanism of action, which is arresting the U138MG, U87, and U373 GBM cell cycle in the G_2/M phase, depolarizing the mitochondrial membranes, releasing cytochrome c, and inhibiting the BCL-xL activity [123]. Tetra-O-methyl-nordihydroguaiaretic acid, a repressor of *Survivin* and *CDK1*, which are the target genes of transcription factor SP1, also induces cycle arrest in the G_2/M phase and apoptosis of GBM cells, suppressing their proliferation [124].

Histone deacetylase inhibitors

HDAC histone deacetylases are involved in the deacetylation of histones H3, H4, H2A, and H2B of ε-N-acetyl-lysine, thereby changing chromatin conformation and suppressing the gene expression. In contrast, HDAC inhibitors (HDACi), such as sodium valproate, enhance gene transcription [125]. Suberoylanilide hydroxamic acid (SAHA) prevents the acetylation and ubiquitination of nucleolin (NCL) (involved in ribosome biogenesis and RNA maturation) through suppression of the JNK/STAT3 signaling pathway, which inhibits the expression of *SOX2, OCT4, BMI1*, and *CD133* genes in GBM stem cells, inhibiting cell proliferation [126, 127]. At high concentrations (more than 5 μM), SAHA induces the activity of caspases 8 and 9 and p53 protein, which trigger apoptosis in GBM stem cells [127]. Another inhibitor, romidepsin (FK228) stimulates the activity of caspase 3, Bax, and Parp proteins and inhibits the Pi3k/Akt/mTOR cascade and BCL2 protein expression, thereby inducing the programmed death of GBM cells. These events enhance the cytotoxic effect of TMZ on GBM cells [128].

RGFP109 inhibitor suppresses the formation of the NF-κB/p65 complex with the coactivators p300- and p30/CBP-associated factor PCAF, which enhances the expression of the growth inhibitor suppressor gene 4 (*ING4*) and suppresses the expression of NF-κB target genes that stimulate progression of GBM [129].

Histone lysine demethylase inhibitors

Inhibitors JIB04 and CPI-455 of histone lysine demethylase (KDM) dephosphorylate AKT, triggering the arrest of the G_2 phase of the cell cycle, autophagy, and apoptosis of GBM cells [130, 131].

Methyltransferase inhibitors

TMZ is a widely used MGMT inhibitor in GBM chemotherapy. The susceptibility of glioma cells to TMZ increases the miR-198 level, which suppresses MGMT expression [132]. miR-198 methylates the *WNT3* promoter, inhibits the Wnt3/Gsk-3β/β-catenin cascade, and binds β-catenin to the *ABCB1* promoter, which suppresses its expression. These events enhance the sensitivity of GBM cells to doxorubicin, vinblastine, and topotecan (P-gp substrates) [133]. NCL protein expression is associated with increased sensitivity of gliomas to TMZ [126]; this chemotherapeutic drug induces autophagy in MOGGCCM glioma cells through activation of the expression of Beclin protein (ATG6) and light chain 3α of microtubule-binding protein-1 (LC3II) and decreasing the level of p62 protein [134]. Meanwhile, overexpression of YB-1, AKT3, MELK, EZH2, and MVP/LRP proteins enhances the resistance of GBM cells to TMZ [135]. AKT hyperactivation induces the expression of SPARC/osteonectin proteoglycan-1 containing cwcv- and kazal-like domains (SPOCK1), which enhances GBM invasion and its resistance to TMZ [136]. This is also facilitated by the action of connective tissue growth factor, which activates the TGF-β1/ERK1/2/Smad cascade and overexpression of the *SOX2, SOX9,* and *HOXA9* genes and the mTOR protein [137]. It is suggested that the transcription factor ZEB1 helps GBM cells resist TMZ, as evidenced by data on the regulation of its expression by miR-200 and ROBO1, c-MYB, and MGMT proteins [138].

Recently, histone methyltransferase G9a inhibitors, such as BIX01294, have been used to treat GBM. This compound suppresses the expression of autophagy proteins LC3B, LC3II, protein 1 containing phosphoinositide-interacting WD repeat domain (WIPI1), and differentiation markers, glial fibrillary acidic protein, tubulin III (TUBB3) in GBM cells, which prevent tumor malignancy [139].

Topoisomerase inhibitors

One of the topoisomerase II inhibitors used in the chemotherapy of brain tumors is etoposide which suppresses livin-α mRNA expression in U251 GBM cells and activates apoptosis [140]. Mitoxantrone, which inhibits the activity of BCRP in LN229 GBM cells, also reduces the expression of topoisomerase II. In turn, the BCRP inhibitor fumitremrergin C can enhance the antitumor effect of mitoxantrone [11]. The inhibitory action of topotecan and irinotecan targets topoisomerase I. Irinotecan translocates the transcription factor YB-1 into the nucleus and enhances the effect of trichostatin A, an inhibitor of histone deacetylase [141].

DNA replication and synthesis inhibitors

Chemotherapy protocols for brain tumors may include the platinum chemotherapy drugs carboplatin and cisplatin. The platinum atom of these chemotherapy drugs forms coordination bonds with guanine bases and alkylating adducts of DNA, which prevent its replication and synthesis, initiating the apoptosis of tumor cells. An increase in the sensitivity of, for example, U373 glioma cells to carboplatin can be noted when the expression of the tyrosinase-related protein (TRP2), BCRP, MGMT, P-gp, MRP1, and MRP3 is inhibited [142]. The use of the JAK2/STAT3 inhibitor JSI-124 enhances the efficiency of the cytotoxic effect of cisplatin on GBM cells [121].

Besides the platinum compounds, bis-chloroethyl nitrosourea (BCNU) and hydroxycarbamide have an alkylating effect on DNA. The expression of the proapoptotic protein lipocalin-2 (LCN2) and Clk1 and the dephosphorylation of Akt increase the sensitivity of glioma cells to BCNU [36, 143]. On the contrary, the overexpression of protein mRNA of the guanine nucleotide exchange factor Rex-1 enhances the proliferation and resistance of GBM cells to BCNU by activating the p38MAPK/JNK and Pi3k/Akt/Gsk-3β signaling cascades, ABCG2 expression, and inhibition of apoptosis [144]. Doxorubicin, which induces the formation of free radicals in the membranes of tumor cells, suppresses DNA synthesis. However, during cyclic hypoxia, overexpression of the *ABCB1* and *ABCG2* genes and hyperactivation of P-gp, BCRP, and HIF-1α enhance the resistance of GBM cells to the chemotherapy drug [145, 146].

Microtubule and proteasome inhibitors

Microtubule and proteasome inhibitors include vincristine and vinblastine which bind to cleavage spindle microtubule tubulin, causing it to rupture and stop tumor cell mitosis. Vincristine at the doses of 10 and 60 nM for one to three days reduces the expression of *ABCB1* mRNA in SF188 cells of GBM [147].

In turn, DSF-Cu inhibits the function of proteasomes and DNA repair, thereby potentiating the effect of DNA alkylating chemotherapy drugs and TMZ on brain tumor stem cells [148].

Conclusion

The overexpression of ABC family transporter proteins causes the GBM cell to resist the targeted and chemotherapy drugs. Targeted drugs used to treat GBM or those under clinical trials are inhibitors of ABC transporters (sunitinib malate, imatinib, elacridar, pantoprazole, statins, verapamil, cyclosporine A, ONT-093, XR9576, and flavonoids), phosphodiesterase-5 (fumitremrergin, indolyl diketopiperazine, and OSU-03012), tyrosine kinase EGFR receptors (cetuximab, panitumumab, gefitinib, erlotinib, and lapatinib), vascular endothelial growth factor (bevacizumab and everolimus), signaling pathway proteins (γ-secretase, voxtalisib, and temsirolimus), transcription factors NF-κB (BAY117082, parthenolide, and MG132) and STAT3 (JSI-124 and STX-0119), histone deacetylases (sodium valproate, SAHA, trichostatin A, romidepsin, and RGFP109), methyltransferase (MGMT) (TMZ), O-6-benzylguanine and histone methyltransferase G9a (BIX01294), histone lysine demethylase (JIB04 and CPI-455), topoisomerases I (topotecan and irinotecan) and II (etoposide), DNA replication and synthesis (carboplatin and cisplatin, BCNU, hydroxycarbamide, and doxorubicin), microtubules (vincristine and vinblastine), and proteasome (DSF-Cu). To develop and create new

highly selective targeted drugs, it is necessary to search for and identify new selective molecular targets in GBM cells. The following can serve as new targets for the action of targeted drugs on ABC transporters: proteins MSI1 and MSI2, p53, TRAIL, MGMT, GRP78, RAB4, RAB5, p19; receptors frizzled, RET, and EGFR; signal transduction and cell cycle kinases JAK1/2, AMPK, WNT5a, MELK, CLK1, GSK-3β, and CDK6; miRNA miR-130a, miR-145, miR-27a, miR-328, miR-200c; transcription factors NRF2, FOXO3a, YB-1, NF-κB, ATF4, CREB, AP-1, ZEB1, and ZEB2; the translation factors eIF2, eIF5, eIF3, and PERK; genes and oncogenes *c-MET, HGF, PTEN, ACCN3*, and *ACCN4*.

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