CHAPTER FOURTEEN

Alkaloids of fascaplysin are promising chemotherapeutic agents for the treatment of glioblastoma: Review

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Abstract

Glioblastoma is one of the most aggressive human brain tumors. Even following all the modern protocols of complex treatment, the median patient survival typically does not exceed 15 months. This review analyzes the main reasons for glioblastoma resistance to therapy, as well as attempts at categorizing the main approaches to increasing chemotherapy efficiency. Special emphasis is placed on the specific group of compounds, known as marine alkaloids and their synthetic derivatives exerting a general antitumor

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effect on glioblastoma cells. The unique mechanisms of marine alkaloid influence on the tumor cells prompt considering them as a promising basis for creating new chemotherapeutic agents for glioblastoma treatment.

1. Introduction

Glial brain tumors invariably stand out among the most deadly types of human cancer. Glioblastoma (GBM) holds a special place among other gliomas as the most frequent and aggressive type of a primary human brain tumor (Lukas et al., 2019). GBM is characterized with fast invasive growth, strong resistance to treatment and unfavorable prognosis. Systemic solution of this problem was found only in the middle of the XX century, and the modern treatment standards are based on the protocols developed by Roger Stupp (Stupp et al., 2005; Stupp, Toms, & Kesari, 2016) and involve extremely rough treatment of GBM.

The recommended treatment for such patients implements a surgery, as well as high dosage of radiation and chemotherapy. Temozolomide (TMZ) is considered to be the main drug for GBM chemotherapy. This recommendation is standard, except for elderly patients with a low Karnofsky performance status. Despite the efforts of medical specialists, the median survival of GBM patients does not exceed 15 months (Lukas et al., 2019; Stupp et al., 2016), and only 25–27% of patients manage to live longer than 2 years since being diagnosed.

The reasons for such insufficient treatment results are associated (Da Ros et al., 2018; Furnari, Cloughesy, Cavenee, & Mischel, 2015; Oberoi et al., 2016) with extreme heterogeneity of GBM cell population, having many poorly differentiated cell elements with high plasticity commonly referred to as cancer stem cells (CSCs). The attempts at increasing the efficiency of GBM chemotherapy by combining TMZ with targeted antitumor drugs was proved to be ineffective after large-scale clinical trials (Touat, Idbaih, Sanson, & Ligon, 2017) which can be due to high polymorphism of proteome maps and transcriptomic landscape of GBM cells (Meyer et al., 2015). Moreover, so-called quiescent CSCs are inherently resistant to chemotherapeutic drugs and can sustain in inactive G0 phase for long term, so they should be activated to make them drug sensitive (Gulaia et al., 2018). This fact points out the necessity for discovering new medication agents able to exert an overall multitargeted effect on GBM cells.

In the light of the abovementioned, we should consider a group of promising pyridodiindols derivatives, known as Fascaplysin alkaloids. These substances exhibit significant cytotoxic and cytostatic effect on GBM cells, making these alkaloids hopeful candidates for developing new glioma medication.

2. Existing standards of glioblastoma (GBM) treatment

The modern standard (Stupp et al., 2016) of complex GBM treatment invariably involves surgical removal of the tumor. This surgery is justified for the majority of patients with almost any type of tumor location in the brain. The main aspect of the treatment is radiation therapy. Patients receive 60 Gy, distributed in 2 Gy daily—30 fractions during 6 weeks, combined with temozolomide (75 mg/m^2/day). Patients' life expectancy correlates with the radiation dose of 60–70 Gy, and further dosage increase does not improve the survival rates, but results in radiation necrosis of the brain and severe neurological and psychological disorders.

The attempts at extending patients' life expectancy are mostly centered on chemotherapy. The recommended treatment protocol involves 6–12 cycles of chemotherapy with temozolomide (TMZ), inducing the G2/M phase cell cycle arrest (Lee, 2016). The first chemotherapy cycle prescribes 150 mg/m2/d on the days 1–5 of the 28-day cycle, increasing the TMZ dosage up to 200 mg/m^2/day in the follow-up cycles. Combining TMZ with radiation therapy allowed to extend the median survival from 7.7 to 13.5 months (Messaoudi, Clavreul, & Lagarce, 2015; Perry et al., 2017). However, increasing the number of chemotherapy cycles, as well as the frequency of TMZ administration, does not significantly affect the rates of patients' life expectancy. Moreover, TMZ therapy proved to be ineffective in 50% of GBM patients (Lukas et al., 2019; Stupp et al., 2016).

Cytotoxic nature of TMZ is determined by methylation of guanine in the DNA at the N7 and O6 positions, as well as of adenine in the O3 position. Damage to genome results in a powerful countereffect, involving direct DNA repair, basic excision DNA repair, homologous recombination and non-homologous end joining. Methylated nitrogenous bases can be eliminated with enzymes, cutting out bases, such as alkylpurin-DNA-*N*-glycosylase (ADG), or dealkylated due to O^6-methylguanine DNA methyltransferase (MGMT). The arsenal of prospective means to suppress the DNA repair is quite scarce (Erasimus, Gobin, Niclou, & Van Dyck, 2016):

Lomeguatrib inhibits the direct DNA repair, Methoxyamine hinders the basic excision DNA repair, Olaparib causes double-stranded DNA break, thus, increasing genome instability and leading to GBM cell death. However, the overall efficiency of these drugs together with TMZ is still similar to TMZ monotherapy.

In this respect, there have been many attempts to combine TMZ with Procarbazine, Lomustine, Carmustine, Nimustine, Fotemustine, Dacarbazine, Irinotecan, Etoposide, Vincristine, Cisplatin, Carboplatin, Paclitaxel and other cytotoxic medication (Lee, 2016; Messaoudi et al., 2015; Stupp et al., 2017). PCV (Procarbazine, Lomustine, Vincristine) and CAP (Cyclophosphamide, Doxorubicin, Cisplatin) regimens have been used less frequently, but their application was shown to have no additional affect over TMZ therapy. Therefore, the scientific community should consider combining TMZ with targeted drugs for increasing GBM chemotherapy efficiency.

3. GBM genetic signatures

The importance of glioma molecular profiling was emphasized by the World Health Organization (WHO), which released new glioma classification in 2016, based on the presence of mutations in tumor protein 53 (TP53), isocitrate dehydrogenases type 1 or 2 (IDH1, IDH2) and 1p/19q codeletion. Thereby gliomas are divided into IDH-mutant (IDHmt) and IDH-wild type (IDHwt), the former are further divided into 1p/19q codeleted or TP53 and ATRX (ATP-dependent helicase ATRX, X-linked helicase II) mutant (Louis et al., 2016).

Gliomas with IDH mutations and 1p/19q codeletion are classified as oligodendrogliomas, while tumors with mutations in IDH1/2, TP53 and ATRX genes—as astrocytomas. IDHwt tumors are identified as primary glioblastomas (Louis et al., 2016). As can be seen, using this classification based on molecular markers, gliomas can be divided into histological subtypes with sufficient accuracy.

In contrast to oligodendrogliomas and astrocytomas, primary GBMs are incredibly heterogeneous in terms of genetics, so it is hardly possible to define marker mutation characterizing the majority of the cells within the tumor, this is why primary GBMs are referred to as IDH-wt. Absence of marker alterations makes it difficult to suggest the cell of origin and to define initiating or driver mutations for primary IDH-wt GBMs. However, GBM still has several common genetic hallmarks allowing to separate them from the rest of gliomas. In this way, mutations in promoter of telomerase

reverse transcriptase (TERT-p) present in up to 90% of adult GBMs (Brandner & von Deimling, 2015; Ceccarelli et al., 2016). TERT-p mutations occur due to substitution of cytosine to thymidine at position 228 and 250 (C228T and C250T; chr5, 1,295,228C > T and 1,295,250C > T, respectively) and lead to generation of binding site for E26 transformation-specific family transcription factor resulting in increased TERT expression (Panebianco, Nikitski, Nikiforova, & Nikiforov, 2019). However, hotspot TERT-p mutations are also present in high frequency in oligodendrogliomas (95%) making them unspecific for GBM definition, although in both cases TERT-p mutations are associated with significantly poor survival (Kim et al., 2018; Lee et al., 2017). TERT-p mutations never coincide with ATRX mutation, which support alternative lengthening of telomeres (Liu et al., 2019).

Other most frequently altered genes in IDH-wt GBMs include CDKN2A (50%); TP53, EGFR, and PTEN (30–40%); as well as CDK4, NF1 and Rb1 (12–15%) (Ceccarelli et al., 2016). Almost half of GBMs harbor missense mutations, rearrangement, altered splicing or amplification of EGFR (Brennan et al., 2013), approximately 50% EGFR-amplified tumors acquire the variant III (EGFRvIII) deletion of exons 2–7 that results in constitutive activation of receptor tyrosine kinase (Appin & Brat, 2015; Verhaak et al., 2010). EGFR variant II (deletion of exons 14–15) also can be found in GBMs with approximate incidence of 9% of focally amplified EGFR cases (Brennan et al., 2013; Chrysanthakopoulos & Chrysanthakopoulos, 2018). Additionally, EGFR can acquire point mutations in the extracellular region, most frequent of which are R108K, A289V/D/T, and G598D occur in 24% GBM samples (An, Aksoy, Zheng, Fan, & Weiss, 2018; Brennan et al., 2013).

Approximately 15–18% primary IDH-wt GBMs carry PDGFRA amplifications while MDM2 and CDK4 amplifications are present in 5–15% and 14–18% of the cases, respectively (Aldape, Zadeh, Mansouri, Reifenberger, & von Deimling, 2015). BRAF V600E mutations are rare in GBMs (Aldape et al., 2015; Behling et al., 2016; Takahashi et al., 2015), but can be associated with better prognosis for patient (Vuong et al., 2018). Interestingly, BRAF V600E never coincides with IDH1/2 mutations but may also define a subgroup of slowly progressing gliomas with better treatment response (Chi et al., 2013). It is clear that in analogous with IDH1/2 mutations BRAF V600E alters cell methylation profiles; however, the reports about extent and mechanism of this methylation changes are controversial (Bond et al., 2018; Hinoue et al., 2009; Hou, Liu, Dong, & Xing, 2012) emphasizing the necessity for further investigation.

It was described that some significant mutations are common for primary GBMs, such as chromosome 7 gain (it carries EGFR one of the most mutated genes in IDH1/IDH2-wt GBMs), chromosome 9p (it contains tumor suppressor genes CDKN2B and CDKN2A) and chromosome 10 (contains PTEN and LGI1, which are responsible for cell growth regulation) loss (Crespo et al., 2011).

IDH1/IDH2-mut primary GBMs occur rarely and they mostly develop from undiagnosed astrocytoma (Ohgaki & Kleihues, 2013), as they carry astrocytoma molecular markers (Liu et al., 2012). Chromosome 10q loss may cause anaplastic astrocytoma transition to secondary GBM, though it's a significance for primary GBM, however its mostly found in secondary GBM (more than 60%) (Ohgaki & Kleihues, 2013).

Approximately, 3% of adult primary GBMs carry H3F3A mutations with K27M being the most frequent. H3F3A mutations and BRAF mutations will be present in tumors that do not have IDH1/2 mutations (Aldape et al., 2015).

Approximately, 34% of glioblastomas contain various mutations of TP53 as well (Brennan et al., 2013). About 95% of all TP53 point mutations are found in the DNA-binding domain (Puca et al., 2011), including the most common mutations found in astrocytomas and glioblastomas: R273C (commonly found in IDH-mt astrocytomas), R273H (commonly found in IDH-wt astrocytomas and glioblastomas) and R175H (Bykov, Eriksson, Bianchi, & Wiman, 2018; Shajani-Yi, de Abreu, Peterson, & Tsongalis, 2018). These alterations also called "gain-of-function" (GOF) mutations as their expression leads to p53 acquiring new prooncogenic features associated with its ability to act as a transcription factor. However, molecular mechanism of carcinogenesis in gliomas with TP53 GOF mutations is understudied, with the exception of the recent publication of Ham et al., which demonstrated an increase in expression of inflammation and chemotaxis genes in ectopic expression of TP53 R248L in glioma cells (Ham et al., 2018).

MGMT promoter methylation is found in almost 50% GBM and associated with longer patient survival and better response to temozolomide (Rivera et al., 2010; Wick et al., 2014). Moreover, progression free survival of GBM patients strongly correlates with the level of MGMT-p methylation, in this way, highly methylated MGMT (>20%) associated with significantly improved patient survival, while in low methylated (10–20%) and unmethylated (<10%) group patients demonstrated the absence of outcome improvement if treated with radiotherapy and TMZ (Radke et al., 2019).

Data from the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) program show that for most glioma patients overall survival has not significantly improved over the past three decades (Davis, Kupelian, Freels, McCarthy, & Surawicz, 2001). Data from other, smaller-scale studies showed a moderate improvement at least for oligodendroglial tumors (Asklund, Malmstrom, Bergqvist, Bjor, & Henriksson, 2015; Crocetti et al., 2012; Ruiz & Lesser, 2009; Sant et al., 2012). In this regard, WHO highlights insufficient development of fundamental aspects of glioma pathogenesis, the lack of a personalized approach to the diagnosis and treatment of patients, the use of outdated methods, technologies and drugs as leading causes for the current problem, which is reflected in resolutions of international consensus (Louis et al., 2014) developed by leading WHO experts.

4. Mutation-based GBM therapy

There is a lack of information about mutation specific therapy for glioblastomas, however, certain mutations shared by different cancer types can underpin the sensitivity to therapeutic agents acting against certain genetic alterations. Thus, we review the possible treatment approaches for the most frequent GBM mutations employed for antitumor therapy in various cancer types.

The most common mutations detected in GBM are TERT-p (85%), CDKN2A (50%), EGFR (30–50%) and PTEN (30%). Although TERT-p mutations are shared with oligodendrogliomas and cannot be suggested as a marker, although their prevalence in GBMs implicates the possible role in tumor initiation. There is no TERT-p specific therapy for gliomas in clinics, moreover, we were able to find only one example of TERT-p specific agent in research level—TG-4260, which is a small chaperon molecule binding to misfolded 5–12 G-quadruplex and restore its silencing function thus abrogating TERT overexpression (Bollam et al., 2018). GTC365, a small molecule-chaperon participating in the G-quadruplex folding and redirect mutant promoter G-quadruplex misfolding, thus reduce hTERT expression (Kang et al., 2016). However, there are several options for TERT silencing explored in lung cancers, for instance, 21-bp hTERT siRNA which suppress telomerase expression on mRNA level. Nevertheless, siRNA approach is far from clinical application due to lack of safe and target-specific carriers for tumor site delivery, although the promising cutting-edge utilizing quantum dots-siRNA nanoplexes makes cancer gene therapy more feasible.

For example, Lin G. et al. have shown that cadmium sulphoselenide/Zinc sulfide quantum dots loaded with siRNA against TERT mRNA can downregulate its expression in glioblastoma cells (Lin et al., 2017). Telomelysin, a human telomerase reverse transcriptase (hTERT) promoter driven modified oncolytic adenovirus, is now in phase II clinical trials, however, the results are not available (Khan et al., 2019), although in phase I trials it showed good tolerability (Nemunaitis et al., 2010). Another gene-based approach for TERT inhibition is the use of an oligonucleotide that blocks the template region of telomerase—GRN163L (Imetelstat), that was shown to limit the lifespan of pancreatic cancer cells (Burchett, Yan, & Ouellette, 2014). The other possible way abrogating TERT expression is to inhibit RAS/MEK signaling pathway regulating TERT, which was shown to be perspective in melanoma cells as NRAS silencing led to TERT downregulation (Reyes-Uribe et al., 2018).

In contrast to TERT-based therapy, there is a plethora of available anti-EGFR strategies for GBMs. There are several therapy approaches, such as small molecules tyrosine kinase inhibitors, monoclonal antibodies, targeted toxins. Among the many agents developed to target the EGFR, the so-called small molecule TKIs interfere with the signal transduction cascade of its tyrosine kinase activity (Caraglia et al., 2006). Despite the enormous amount of the developed therapeutics for tyrosine kinase inhibition, there are still no clinically approved compounds for GBM treatment, which is possibly due to lack of specificity of these molecules and redundancy in growth and proliferation pathways. Thus, erlotinib, gefitinib, and lapatinib showed very limited efficacy and side effects as a single agent and in combination with other anticancer agents in newly diagnosed glioblastoma (Westphal, Maire, & Lamszus, 2017). Afatinib has shown only limited efficacy in a clinical trial in patients with recurrent glioblastoma (Reardon et al., 2015) and several long-term responses when combined with temozolomide and radiation therapy in newly diagnosed GBM (Saran et al., 2018). Additionally, afatinib in combination with temozolomide was shown to target EGFRvIII-cMet signaling in GBM cells (Vengoji et al., 2019). Lapatinib has shown very limited efficacy as a single agent in recurrent glioblastoma (Iwamoto et al., 2010), and high rates of adverse effects (lymphopenia) when administered high pulse-dose for better brain penetration (Yu et al., 2017).

The second approach employing the use of monoclonal antibodies is described in Section 5.

EGFRvIII is not responsive to clinically approved antibodies as they mostly targeting the L2 domain deleted in this truncated EGFR. mAb806 (ABT-806), a monoclonal antibody which is able to bind EGFRvIII recognizing its 806-epitope (Orellana et al., 2019), was shown to ignore EGFR on

normal cells and well tolerated in GBM patients (Cleary et al., 2015). Another approach to target EGFRvIII was conducted using modified T cells expressing chimeric antigen receptor in patients with recurrent GBM. All patients demonstrated modified T cells are capable of traffic to the tumor site, however, only one patient had residual stable disease for over 18 months (O'Rourke et al., 2017).

Most drugs designed for specific treatment of p53 mutant tumors can be divided into two subtypes: (1) drugs that increase expression/function of normal p53, and (2) drugs that reduce mutant p53 expression. First group includes substances such as: CP-31398 (styrylquinazoline), which stabilizes DNA binding component and native conformation of non-mutant p53 (Tanner & Barberis, 2004); STIMA-1 (Zache et al., 2017) and PRIMA-1, which not only increase stability of the non-mutant p53, but also restore the DNA binding activity of the mutant p53R175H, leading to of MDM2 and p21 expression (Lambert et al., 2009). Additionally, this group includes substances such as MIRA-1 and its structural analogs (Bykov et al., 2005), NSC652287/RITA, which restore transcriptional activity of non-mutant p53 (Burmakin, Shi, Hedstrom, Kogner, & Selivanova, 2013); NSC319726/ZMC1 (Puca et al., 2011), Stictic Acid (Wassman et al., 2013), P53R3 (Weinmann et al., 2008) and Chetomin, which acts specifically on cells expressing p53R175H (Hiraki et al., 2015). However, despite the diversity of these substances, PRIMA-1MET is currently the only substance undergoing clinical trials, indicating that the development of drugs reactivating non-mutant p53 requires more thorough screening conditions during the in vitro testing phase. Another promising compound, arsenic oxide (III), was shown to activates proteasome degradation of p53 (Yan, Jung, Zhang, & Chen, 2014).

Apart from small molecules and drugs, increasing attention is attracted to the development of gene therapy, specifically transducing of normal p53 gene. There are already two clinical trials investigating this approach for cancer treatment. For example, recombinant adenovirus-p53, which is an E1 substituted replication-disabled recombinant adenovirus encoding the human p53 gene, was shown to overcome the surgery and chemoradiotherapy in terms of overall survival rates for hypopharyngeal squamous cell carcinomas patients (Biaoxue, Hui, Wenlong, & Shuanying, 2016; Liu et al., 2018) and for patients with nasopharyngeal carcinoma (Yuan, Xu, & Chen, 2016).

Interest in the development of compounds from second group, inhibitors of mutant p53 function or expression, is based on two facts: (1) mutant p53 is inherently unstable, potentially accelerating tumor progression

because of stabilization (Terzian et al., 2008) and (2) using small interference RNA (siRNAs) or shRNAs to knockdown mutant p53 reduces malignant properties of cancer cells (Alexandrova et al., 2015). Second group includes heat shock protein 90 (Hsp90) inhibitors—geldanamycin, 17-AAG, and ganetespib—which destabilize and degrade a variety of different p53 mutant forms (p53R175H, p53L194F, p53R273H, p53R280K) (Li, Marchenko, Schulz, et al., 2011; Ramalingam et al., 2015), and histone deacetylase inhibitors—vorinostat/SAHA, romidepsin/depsipeptide, which inhibit mutant p53 transcription by inhibiting histone deacetylases 6 and 8 (HDAC6 and HDAC8) (Li, Marchenko, & Moll, 2011; Yan et al., 2013). Many of these compounds are currently undergoing clinical trials. However, it's already known that a promising Hsp-90 inhibitor ganetespib failed at the third phase of clinical trials, without demonstrating significant increase of progression free survival (PFS) (Pillai, Fennell, & Kovcin, 2016). Inhibitor of histone deacetylase—vorinostat, also failed to demonstrate efficacy in glioblastoma patient trials (Ghiaseddin et al., 2018). Arsenic (III) oxide showed very promising results. However, its being studied almost exclusively as an agent for hematological tumor therapy (Efficace et al., 2014; Jain, Konoplev, Benjamini, Romagura, & Burger, 2018; Yanada et al., 2013). It is also not clear whether these compounds influence other molecular pathways, whether they affect all types of p53 mutations or how their specificity may be limited.

A separate group consists of natural extracts and substances that have selective activity against prooncogenic mutant isoforms of p53. Natural substances have a great advantage over synthetic molecules in terms of lower total toxicity allowing for their qualitative combination with chemotherapy without increasing side effects. However, without chemical modification to extend their half-life and improve their penetrating ability, effectiveness and selectivity of these substances is usually quite low. Nevertheless, development and screening of natural compounds is a promising approach for isolating new biomolecules with an unknown mechanism of action. Identification of natural compounds that affect mutant p53 are still poorly explored. Recently, it has been reported that tryptolide (Carter, Bischof, Dejean, & Vousden, 2007) reduces the expression level of mutant p53 in breast cancer cells MDA-MB-231 (Liu et al., 2009). Also, extract from the terrestrial plant Brachylaena ramiflora, N37063, can inhibit the reduction of the anti-oncogenic activity of p53 in the mutations R175 and R273, as well as induce the expression of p53 gene targets (Karimi et al., 2010). It was found that dietary flavonoid eupatilin induces the G2/M cell

cycle arrest in Hec1A cells by reducing expression of mutant p53, which leads to an increase in p21 expression (Cho et al., 2011). However, neither N37063 nor eupatilin were further investigated in animal models expressing a specific mutant p53.

Fucoxanthin (Bohlman & Manfredi, 2014), a natural carotenoid, inhibits cell growth and colony formation, induces cell cycle arrest at G0/G1 and sensitizes tumor cells to apoptosis (Wang et al., 2014). Fucoxanthin inhibits p53-mortalin complex and enhances p21 signaling. It was found that nonpurified turmeric extract (*Curcuma longa*) and its bioactive component, curcumin, induce apoptosis and autophagy in epidermoid cancer A431 cells expressing p53 R273H (Thongrakard et al., 2014). Both turmeric and curcumin induce macroautophagy, which leads to mutant p53 degradation. Screening in vitro study of small molecules has shown that hetomin (Rayburn, Ezell, & Zhang, 2009) can inhibit the mutant p53 R175H by binding with heat shock protein Hsp40 (Hiraki et al., 2015).

Thus, mutation-based GBM therapy is a rapidly developing and promising field, although the inherent genetic heterogeneity of GBM cells hampers univocal solution, there is a possibility to find a common denominator considering the molecular pathways hijacked by the most frequent GBM mutations. Gene based therapy as well as natural compounds are currently the forefront as the former can provide etiotropic treatment, and the latter possess low toxicity enabling simultaneous chemopreventive and chemotherapeutic effect.

5. Targeted GBM therapy and ways of increasing its efficiency

Growth factors that are crucial for GBM pathogenesis were one of the first molecules in targeted chemotherapy. More than 60% of GBMs have overexpression of epidermal growth factor receptor (EGFR). Amplificating EGFR gene is typical for GBM and coincides with a loss of heterozygosity in chromosome 10q. This mutation is related to the loss of PTEN gene function suppressing intracellular signal transmission in PI3K/AKT/mTORb. Tipifarnib, Erlotinib and Lapatinib have been suggested for this growth pathway inhibition (Li, Zhang, An, & Ma, 2016). Additionally, Imatinib, Temsirolimus and Everolimus have been used to suppress the tyrosine kinase activity of thrombocyte growth factor (Cantanhede & de Oliveira, 2017). Bevacizumab that antagonizes vascular endothelial growth factor is the most vastly used agent. The latter one has shown the most promising results

(Diaz et al., 2017) in a series of clinical trials, while in combination with TMZ, Bevacizumab was proved to be more efficient than the standard chemotherapy (Stupp et al., 2016).

DNA methylation is a fundamental mechanism of deactivating genes in eukaryotic cells. GBM is characterized with a generally low level of DNA methylation (50% lower than in normal brain tissue), moreover hypomethylation of relapse GBMs is significantly higher than in the primary lesions. Therefore, TMZ was combined with therapeutic agents affecting epigenetic regulation of gene expression, such as Vorinostat (Galanis et al., 2018), Romidepsin, Azacytidine, and Decitabine, to investigate if this would result in better performance. In addition, Clofazimine, Regorafenib, Nigericin, Monensin, Salinomycin, Niclosamide, and Silibinin have been suggested for suppression of Wnt signaling pathway in GBM cells (Lyakhova et al., 2018). However, it should be noted (Touat et al., 2017) that almost all new drugs, suggested for GBM treatment, proved to be relatively ineffective in large clinical trials, and even the new targeted drug—Rindopepimut (Weller et al., 2017)—has not met the expectations.

The most probable reason causing the failure of the existing therapy methods is the poor penetrability of the blood-brain barrier (Da Ros et al., 2018; Drean et al., 2016; Oberoi et al., 2016). Even though its integrity is compromised both due to GBM development, and surgical intervention (Kane, 2019; Vick, Khandekar, & Bigner, 1977; Wen et al., 2017), the studies conducted with gadolinium contrast agents revealed accumulation of these substances only in some parts of the tumor (Sarkaria et al., 2018), while the areas of active tumor cells proliferation outside the primary lesion were completely protected by the blood-brain barrier and remained almost inaccessible for chemotherapeutic agents. Undoubtedly, the modern technologies of targeted drug delivery through the blood-brain barrier (Sharma, 2011; Sharma, Muresanu, Mossler, & Sharma, 2012) manage to overcome this issue to some extent.

Nevertheless, heterogenic nature of GBM cell population remains the main complication (Meyer et al., 2015). Neoplastic cells, isolated from different parts of the tumor, exhibit a wide range of immunohystochemical markers of the cell surface, different proliferation speed and susceptibility to hypoxia, radiation, and TMZ (Furnari et al., 2015; Meyer et al., 2015). Moreover, the cells, obtained from the same tumor biopsy and separated according to the expression of a certain marker on the cell surface (Flavahan et al., 2016), show significant differences in transcriptome and proteome maps. In this respect, the widely discussed idea of using a customized

targeted therapy to eliminate residual glioma cells by means of their molecular and genetic signatures so far has limited practical value due to GBM high heterogeneity.

Based on the abovementioned feature of GBM, the significant prolongation of patients' life expectancy is even theoretically impossible with selective targeted monotherapy. A combination of drugs can simultaneously affect the majority of relevant targets, destroying the larger part of the tumor cells, however dramatically increasing the probability of severe side effects due to combination toxicity. This warrants significant efforts for seeking the substances contemporary affecting the key components of several molecular cascades, involved in pathological changes of cancer cells, which may become a new generation of multitargeted medication.

6. Fascaplysin alkaloids and their antitumor properties

In the light of the abovementioned, our attention was brought to the group of small molecules, based on pentacyclic system of pyrido[1,2-a:3,4-b′]diindol. The most well-known part of this group is Fascaplysin, a red pigment (Fig. 1), first extracted from the sponge *Fascaplysinopsis* sp. in 1988. Fascaplysin has a wide range of biological properties. Its antitumor effect is based on the ability to inhibit the important kinases, participating in the main phases of GBM cell life cycle (Hamilton & Infante, 2016), to affect the PI3K/AKT/mTOR signaling pathway, suppress angiogenesis (Oh et al., 2017), trigger apoptosis and autophagy (Kumar et al., 2015). The majority of Fascaplysin molecular targets are directly involved in proliferation, migration and invasive activities of GBM cells (Jin et al., 2019).

Cyclin-dependent kinase 4 (CDK4) is an enzyme of serine/threonine protein kinases class that together with cyclin-D1 deactivates the retinoblastoma protein (pRB), hence activating E2F genes that code the synthesis of transcriptional factors, necessary for DNA replication and cell cycle

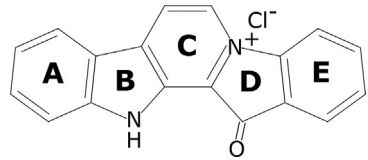

Fig. 1 The structure of fascaplysin. Rings A, B, C, D, E represent unified conjugate system.

progression. The malfunctions of this molecular pathway were discovered in the majority of oncologic diseases (Hamilton & Infante, 2016; McNamara, Sahebjam, & Mason, 2013), and frequently GBM cells exhibit hyper-expression of cyclin D1 and lower level of 16INK4A and RB oncoprotein activity. That is why researching selective CDK4 inhibitors is a priority objective.

The Fascaplysin ability to inhibit CDK4 could be considered a proven fact. In 2017, Chinese researchers demonstrated this effect with Western blotting, along with its other abilities, like apoptosis triggering, lower proliferation and migration activity and cell cycle arrest (Chen et al., 2017) for cancer cells in G0/G1 phase when CDH4 was inhibited with Fascaplysin.

The effect of Fascaplysin on other CDKs is uncertain (Bharate, Manda, Mupparapu, Battini, & Vishwakarma, 2012), since it has exhibited more compatibility with CDK4/cyclin D1 complex, than with CDK6/cyclin D1. At the same time, Fascaplysin inhibits CDK6/cyclin D2, but does not affect CDK4/cyclin D2 and CDK4/cyclin D3 complexes. This fact might be due to cyclins joining CDKs with different regioselectivity, thus, creating several geometric modifications of the active complex site, that has been proven by the results of molecular docking (Shafiq, Steinbrecher, & Schmid, 2012).

The chemical composition of Fascaplysin has quaternary nitrogen in two aromatic rings C and D that is in close proximity to E144-CDK4 area and significantly contributes to Coulomb interaction between carbonyl and NH-groups, creating a donor-acceptor bond with the area, connecting N- and C-end domains of this enzyme. Such special interactions are typical for many CDK inhibitors (Shafiq et al., 2012), and probably are one of the most important mechanisms of their biological activity.

Selective effect on CDK4 activates another molecular cascade, involved in GBM pathogenesis. GBM cells express c-Met or hepatocyte growth factor receptor, having a high level of tyrosine kinase activity in relation toward nuclear transcription factor-κB (NF-κB) that regularly is inhibited by the phosphorylated RB protein. In case of using CDK4/6 inhibitors RB proteins do not suppress NF-κB activity that stimulates synthesis of hepatocytes growth factor (HGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and other cytokines, hyperactivating c-Met receptor and eliminating chemotherapy effects (Olmez et al., 2018).

Our team demonstrated the Fascaplysin ability to cause apoptosis in GBM cells (Bryukhovetskiy et al., 2017). 2 μmol of Fascaplysin showed cytotoxic effect in GBM cells that exceeds the similar results of TMZ.

When lowered to 0.5 μmol of Fascaplysin, its cytotoxic effect decreased, while the created cytostatic effect intensified after longer exposure.

Apoptosis, related to activating caspase-3 and -9, is one of the main mechanisms of Fascaplysin cytotoxic effect. The research of 2015 (Kumar et al., 2015) showed the Fascaplysin ability to induce cell apoptosis, by activating caspase-3, and, consequently, cleavage of Poly [ADP-ribose] polymerase (PARP-1), as well as to trigger autophagy signals, suppress three main components of PI3K/AKT/mTOR signaling pathway (Meng et al., 2019), increase p8 protein and reactive oxygen species (ROS) content in cancer cells, decreasing mitochondrial membrane potential.

Fascaplysin deserves special attention due to its ability to inhibit such crucial molecular targets as VEGFR (Chen et al., 2017; Lin, Yan, & Chen, 2007; Oh et al., 2017; Zheng et al., 2010). For instance, hepatocellular carcinoma BeL-7402 cell line was used to prove that Fascaplysin suppressed the expression of two crucial angiogenesis factors: vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) (Lin et al., 2007). Based on the abovementioned facts, it is not surprising that Fascaplysin exhibited stronger antitumor effect than Abemaciclib and Palbociclib on several cancer cells of different types. Anti- tyrosine kinase activity of Fascaplysin has also been proven (Oh et al., 2017).

There is another aspect of Fascaplysin physiological activity, and it is the aromatic system of pyrido[1,2-a:3,4-b′]diindol that makes it a powerful DNA intercalator. In other words, flat structures are created among nitrogenous bases and stop transcription and translation processes, as shown by the research (Hormann, Chaudhuri, & Fretz, 2001) with calorimetric titration, adsorption spectroscopy and circular dichroism with DNA sample from calf thymus.

Therefore, Fascaplysin is a unique prototype of a revolutionary multitargeted drug for heterogeneous glial brain tumors treatment. One disadvantage of this substance, not unlike the majority of chemical compounds with genotoxic activity, is its relatively high toxicity. The current work in progress is the development of compounds with structural properties of Fascaplysin that determine its enzyme-inhibiting abilities, and having stronger antitumor effect with lower toxicity level.

7. New prospective derivatives of Fascaplysin alkaloids

It is currently known that there are compounds among Fascaplysin derivatives which are not inferior in their antitumor effect, and even having

superior properties. In 2004 12 Fascaplysin alkaloids were tested (Segraves et al., 2004) on different lines of mice and human cancer cells to demonstrate their activity and selective effect. The results showed that even with the same activity level as Fascaplysin, 10-bromofascaplysin is more selective in some human tumors, e.g. breast cancer cells. Cytotoxic effects of Fascaplysin, 3-bromofascaplysin and Homofascaplysin A were compared (Zhidkov et al., 2007), showing that Homofascaplysin A was more active than the original compound in the majority of cancer cell lines, used in the experiment.

In 2007 the Far Eastern Federal University research team synthesized line of Bromofascaplysins (Zhidkov et al., 2007). Different cancer cell lines were used to show that these compounds were indirectly involved in initiating apoptosis, related to activation of caspase-3, -8 and -9 (Kuzmich et al., 2010). Flow cytometry, soft agar method and Western blotting were used to study those mechanisms. Theoretically, these compounds could be used as prospective antitumor drugs.

Our research team synthesized and compared the antitumor effect of some Fascaplysin derivatives (Lyakhova et al., 2018; Zhidkov et al., 2007), namely 7-phenylfascaplysin, 3-chlorofascaplysin, 3-bromofascaplysin and 10-bromofascaplysin, with the effect of the original compound (Fig. 2). As the study indicates, all Fascaplysin derivatives proved their ability to modify the life cycle phases of GBM cells, and the amount of viable cancer cells in G0 phase was at its lowest by the end of the experiment due to 3-bromofascaplysin and 7-phenylfascaplysin. The same derivatives demonstrated the highest level of cytotoxic activity (Lyakhova et al., 2018).

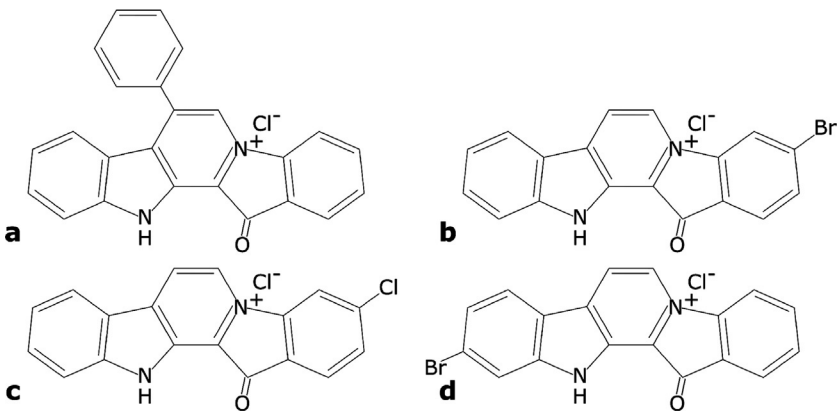

Fig. 2 Derivatives of fascaplysin (A) 7-phenylfascaplysin (B) 3-chlorofascaplysin (C) 3-bromofascaplysin (D) 10-bromofascaplysin.

The research of 2019 tested 3-bromofascaplysin and 3,10-dibromofascaplysin on human melanoma, intestinal and prostate cancer cell cultures. The research showed that 3,10-dibromofascaplysin was highly selective about affecting cancer cells in comparison with normal ones (Zhidkov et al., 2019). Another 2019 example of significant results in this area is the research, conducted by Chinese scientists who studied the approaches to Alzheimer's disease (Pan et al., 2019). Fascaplysin and some of its methyl- and carboxy derivatives showed their cholinesterase-inhibiting powers and neuroprotective properties. More importantly, the ability of 9-methylfascaplysin to penetrate the blood-brain barrier and accumulate in the brain (Hu et al., 2019) shows very high potential for future applications.

8. Conclusion

Prognosis for GBM patients remains unfavorable. This paper aimed at giving a critical analysis of the existing methods of GBM treatment, modern algorithms of antitumor therapy and their obvious downsides. The special emphasis is placed on heterogenic nature of GBM cell population as the main reason of inefficient GBM treatment. Monotargeted chemotherapy has been presented as unable to hinder GBM progression, and a new approach to discovering medical agents with integral multitargeted activity has been argued.

The data on stronger antitumor effect of Fascaplysin derivatives in comparison with the natural substance show the potential of researching various compounds of this group. The ability to penetrate the blood-brain barrier and the effect they have on key enzymes, involved in the majority of oncobiological processes, allow considering Fascaplysin alkaloids as prospective compounds to be used in GBM therapy.

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