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A «Trojan horse» for glioblastoma: targeted aptamer delivery strategy

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ABSTRACT
Gliomas are among the most aggressive primary brain tumors characterized by extremely poor prognosis. Despite standard therapy including surgery, radiotherapy and chemotherapy, median survival remains extremely low. The main obstacles to effective treatment are tumor heterogeneity, blood-brain barrier and difficult targeted delivery of therapeutic agents. This review examines potential of aptamers as an alternative to traditional approaches. A particular attention is paid to mechanisms of aptamer cross-breeding and cellular internalization, particularly receptor-mediated endocytosis. The last one is essential for efficient penetration of these molecules into tumor cells. Analysis of current data demonstrates that aptamers specific to glioma cell surface markers not only provide highly accurate tumor imaging but also open new opportunities for target delivery of therapeutic agents. It is a promising tool for personalized glioblastoma therapy.

Keywords: *aptamers, gliomas, endocytosis.*

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Introduction

Gliomas are the most common primary malignant tumors of the central nervous system (CNS) in adults accounting for approximately 17% of all primary CNS neoplasms [1—3]. Despite standard treatments, including maximally safe resection of tumor followed by radio- and chemotherapy, prognosis for patients remains extremely poor. Median overall survival rarely exceeds 15—20 months, and 5-year survival remains extremely low (<7%) [4—6].

These unfavorable outcomes are due to some factors including tumor heterogeneity and presence of cells with different aggressiveness and oncogenes, difficult delivery of drugs across blood-brain barrier (BBB) and no targeted drugs capable of acting exclusively on tumor cells without damage to healthy cells [7—10]. Therefore, new approaches to diagnosis and treatment of gliomas remain a key challenge in modern science and medicine.

A promising approach is aptamers (synthetic single-stranded DNA or RNA oligonucleotides specifically binding to targets through unique three-dimensional structure). These molecules often referred to as chemical antibodies offer several advantages over traditional antibodies. These are significantly smaller size (approximately 5—10 times smaller than antibodies), high penetrating ability, available precise synthesis with high reproducibility in laboratory and low immunogenicity [11, 12].

An important property of most aptamers is their ability to penetrate BBB that makes them particularly perspective for the treatment and diagnosis of CNS diseases [13, 14].

Successful function of aptamers implies not only reaching the tumor cell and binding to the target molecule on its surface, but also penetrating the cell. Primary mechanism underlying this process is receptor-mediated endocytosis. This endocytosis, also known as clathrin-mediated endocytosis, is a specific uptake process when membrane receptors interact with ligands. This interaction initiates local invagination of membrane resulting in intracellular vesicle [15, 16]. Mechanisms of aptamer endocytosis offer potentials for highly effective delivery of therapeutic compounds to glioma cells.

This review summarizes current data on aptamers in diagnosis and treatment of gliomas with emphasis on mechanisms of their targeted delivery to tumor cells and cellular internalization processes, particularly receptor-mediated endocytosis.

Characteristics of gliomas as targets for aptamer therapy

Gliomas, especially high-grade gliomas, are characterized by cellular and molecular heterogeneity that complicates effective antitumor therapy. The WHO classification of CNS tumors (2021) embraces an approach combining histological and molecular characteristics of neoplasms [17, 18]. This approach is valuable not only to refine classification, but also to predict tumor behavior and identify potential targets for further targeted therapy.

The main molecular markers include mutations in isocitrate dehydrogenase 1 and 2 (*IDH1*/*IDH2*) genes, 1p/19q codeletion and *MGMT* gene methylation. However, alterations in genes involved in key cellular signaling pathways are of greater interest for therapy. Thus, epidermal growth factor receptor (*EGFR*) mutations, particularly the most common *EGFRvIII* variant, can stimulate proliferation and enhance aggressive behavior and survival of tumor cells. Aberrant activation of platelet-derived growth factor receptor (*PDGFR*) pathway and inactivation of p53 tumor suppressor gene (*TP53*) may contribute to aggressive tumor growth. Telomerase activation due to *TERT* mutations maintains telomere stability and tumor cell immortality [18, 19].

Importantly, there is a fundamental difference between diagnostic and therapeutic approaches. Specific binding of molecule to cell surface or its penetration into tumor cell is often sufficient for diagnosis. However, effective therapy requires not only compound delivery to the cell but also initiation of specific intracellular cascades. The last one may be achieved by binding to target molecules on cellular surface and inside tumor cell. However, tumors are characterized by high heterogeneity, and clones within a single tumor can express different combinations of surface markers. This complicates monoclonal therapy, as cells not expressing target molecules evade therapy and lead to recurrence. Aptamers offer a unique solution to this problem thanks to multispecific construction capable of simultaneously binding to multiple targets. This approach allows for simultaneous recognition of many clones and targeting of multiple signaling pathways. Furthermore, high specificity of aptamers enables them to distinguish between similar protein isoforms minimizing potential negative effects. For example, some aptamers can distinguish *EGFRvIII* predominantly found in tumors, while sparing *EGFR* widespread in healthy tissue [20, 21].

Even before molecules reach tumor cells, they encounter a critical obstacle significantly limiting any approach to glioma diagnosis and therapy (blood-brain barrier). BBB strictly controls penetration of substances from systemic circulation into central nervous system and almost completely blocks entry of any large-molecular compounds. Aptamers are much smaller (8—15 kDa) compared to widely available antibodies (150 kDa) and easily penetrate brain parenchyma and glioma cells **(Figure)** [13, 22, 23].

Thus, the key molecular and pathological features of gliomas (tumor heterogeneity and BBB) significantly limit the effectiveness of standard therapeutic approaches, but also make aptamer platforms feasible for diagnosis and therapy. The ability of aptamers to cross the blood-brain barrier and provide highly specific binding to target molecules makes them perspective candidates for new therapeutic approaches.

Aptamers: properties, production and advantages as theranostic agents

Aptamers are synthetic single-stranded RNA or DNA oligonucleotides that can highly specifically with high affinity bind to various targets through folding into unique three-dimensional structures.

Aptamer producing technology (Systematic Evolution of Ligands by EXponential enrichment, SELEX) is based on cyclic selection of molecules from a library of unique oligonucleotide sequences followed by amplification of molecules demonstrating specific binding to certain target [24].

The advantage of this method is available selection of aptamers against almost any biological target, including weakly immunogenic molecules.

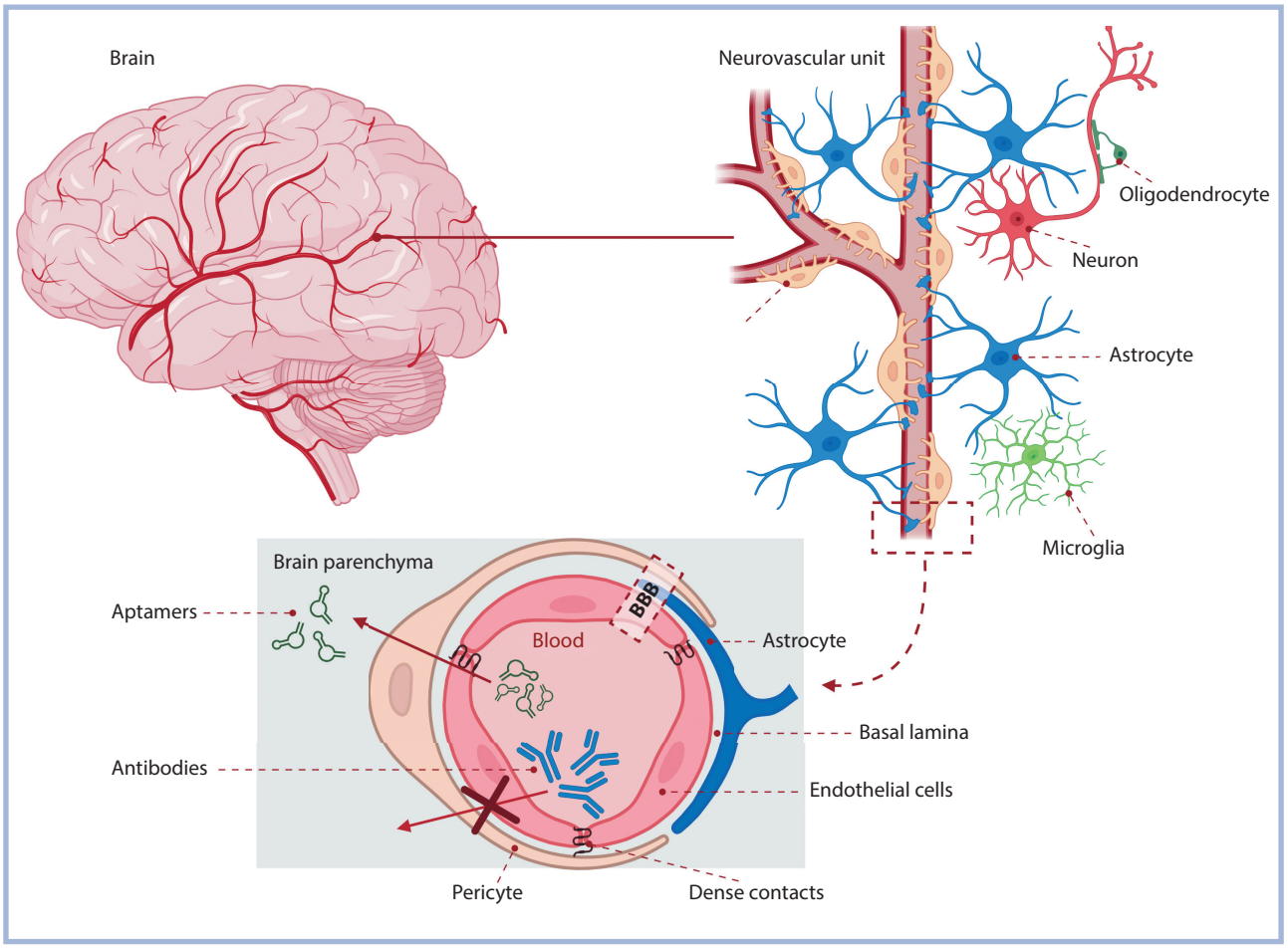
Aptamers offer several advantages over monoclonal antibodies that make them perspective theranostic agents. Unlike antibodies, aptamers are characterized by significantly higher tumor penetration ability due to small size, and available chemical synthesis eliminates manufacturing variability [25, 26].

Another important feature of aptamers is their high specificity with recognition of individual epitopes and functional groups in target molecules. Low immunogenicity of aptamers minimizes the risk of adverse immune reactions and distinguishes them from antibodies. Furthermore, aptamers demonstrate good stability during storage and transportation, as well as offer a wide range of chemical modifications for conjugation with fluorescent labels, therapeutic agents, and nanoparticles [25, 27] **(Table)**.

These advantages of aptamer platform create new opportunities for glioma therapy, but their effectiveness is related to mechanisms of cellular uptake.

Mechanisms of aptamer endocytosis. Receptor-mediated uptake of aptamers by glioma cells

Internalization into the target cell is the main stage of aptamer's biological function. Receptor-mediated (clathrin-mediated) endocytosis is currently the most studied and probable mechanism for aptamer penetration into cells. This process begins with specific binding of aptamer to cell surface receptor, such as *EGFR*. Ligand-receptor complex activates recruitment of adaptor protein AP2 and clathrin on cytosolic side of cellular mem-



Structural organization of blood-brain barrier and its selective permeability for aptamers (created with iorender.com).

Comparative characteristics of DNA aptamers, RNA aptamers, and antibodies

Variable	DNA aptamers	RNA aptamers	Monoclonal antibodies
Molecular nature	Single-stranded DNA	Single-stranded RNA	Proteins
Size, kDa	8—15	8—15	~150
Immunogenicity	Low	Low	High
Tissue penetration	High	High	Low
Production	Chemical synthesis, reproducible	Chemical synthesis, reproducible	Biosynthesis, variable
Production cost	Low	Medium	High
Modification	Wide range of chemical modifications	Limited modification options	Conjugation with drugs
Targets	Cells, proteins, small molecules	Cells, proteins, small molecules	Predominantly proteins
Storage stability	High	Medium	Special conditions required

brane that triggers membrane invagination and formation of clathrin-mediated pit. At the next stage, dynamin contraction ensures vesicle detachment from membrane with subsequent dissociation of clathrin coating. Finally, vesicle becomes early endosome [15, 28].

The fate of internalized aptamers is determined by sorting processes in endosomal compartment. Most of these molecules are targeted to lysosomes for subsequent degradation. However, some aptamers are capable of reaching the cytosol or other intracellular targets via "endosomal escape" mechanism. According to some studies, aptamers targeting *EGFRvIII* are successfully internalized into glioblastoma cells primarily via clathrin-mediated endocytosis [29, 30].

Receptor-mediated endocytosis is important not only in cellular uptake of aptamers but also in regulation of intracellular signaling. In particular, internalization of aptamer-receptor complex can downregulate signaling pathway associated with this receptor. This provides aptamers

with a distinct therapeutic function unrelated to the delivered receptor [31, 32].

Research of molecular mechanisms of aptamer endocytosis offers potential for target therapeutic platforms capable of simultaneous specific transportation of drugs and effect on oncogenic signaling pathways in glioma cells.

Aptamers in glioma diagnosis and therapy

Modern diagnostic methods for gliomas, such as computed tomography and magnetic resonance imaging, have several significant limitations, including insufficient specificity and low resolution in determining tumor boundaries, especially in case of diffuse growth.

One can overcome these challenges using high affinity and specific binding of aptamers to molecular markers on glioma cell surface. This will enable tumor imaging with exceptional accuracy [33—35]. One of the areas is intraoperative visualization. In vivo studies demonstrated high accuracy in visualization of tumors with fluorescently labeled DNA aptamer Gli-233. This aptamer was nontoxic and allowed for clear differentiation of tumor tissue from surrounding brain parenchyma that was crucial for total resection [35].

However, the most interesting area is therapeutic use of aptamers in gliomas. The main pathways for targeting tumor cells include targeted delivery of chemotherapeutic agents, direct inhibition of oncogenic signaling pathways and introduction of entirely new methods, such as differentiation therapy.

Targeted delivery of chemotherapeutic agents

Aptamers are used for targeted delivery of antitumor drugs to glioma cells. These molecules are specific for receptors on tumor cell surface and covalently linked to chemotherapeutic agents such as doxorubicin. This conjugate accumulates primarily in the tumor site, minimizes the impact on healthy tissue and significantly reduces systemic toxicity typical for traditional chemotherapy [11, 36].

Therapeutic effect of aptamers

Some aptamers themselves exert antitumor activity without conjugation to toxic agents. These aptamers bind to receptors essential for tumor cell proliferation and survival, such as *EGFR*, *PDGFR*, and *PARP1*, and block oncogenic signaling. This slows tumor growth, reduces its invasiveness and can increase sensitivity of glioma cells to radio- and chemotherapy [23, 37, 38].

Differentiation therapy

An innovative treatment approach involves aptamers not for tumor cell destruction, but for their reprogramming. This allows the drugs to target immature rapidly dividing glioma cells and stimulate their maturation (differentiation). After this process, these cells lose ability to divide uncontrollably [39, 40].

Conclusion

Modern researches confirm high potential of aptamers for new antitumor drugs. The key advantages of this technology (high binding specificity, penetration through blood-brain barrier, low immunogenicity and easy production) give it a significant advantage over traditional biological drugs.

Mechanism of cellular internalization is one of the key factors determining the effectiveness of aptamers. Recent studies indicated that receptor-mediated endocytosis is the most likely mechanism for aptamer penetration into glioma cells. Understanding the mechanism of this process opens up prospects for target creation of aptamer platforms capable of not only effective delivery of therapeutic agents, but also direct antitumor effect.

Author contribution:
Concept and design of the study— Fab L.V., Pavlova G.V.
Collection and analysis of data — Fab L.V., Dzarieva F.M., Pavlova S.A.
Statistical analysis — Pavlova S.A.
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