Folate Receptors’ Expression in Gliomas May Possess Potential Nanoparticle-Based Drug Delivery Opportunities

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ABSTRACT: Brain cancer affected around estimated 23,890 adults and 3,540 children under the age of 15 in 2020. The chemotherapeutic agents that are already approved by the FDA for brain cancer are proving to be not highly effective because of the interference from the tumor microenvironment as well as their own toxicities. Added to this is the impedance presented by the extremely restrictive permeability of the blood brain barrier (BBB). Targeted nanoparticulate drug delivery systems offer a good opportunity to traverse the BBB and selectively target the tumor cells. Folate receptors are found to be one of the most useful targets for drug delivery to the brain. Hence, this Mini-Review discusses the folate receptors and their application in the treatment of brain cancers using targeted nanoparticles.

INTRODUCTION

As researchers task themselves with the challenge of combating and inhibiting the growth of cancerous cells in the brain, many are left with one of the primary difficulties associated with therapeutics: identifying a drug-delivery system in which cancer cells are selectively inhibited while simultaneously preserving noncancer cells. This problem presents itself quite urgently when one considers neurons' inability to regenerate when damaged. Without proper investigation into how exactly a drug impacts the surrounding tumor microenvironment, certain drugs may pose a greater threat toward the brain’s health because of their toxicity profiles. However, with brain cancer affecting an estimated 23,890 adults and 3,540 children under the age of 15 in 2020 alone, patients are in need of treatments that will support, rather than cause detriment to, their bodies and overall health. 4 In order to minimize the adverse risks of anticancer therapies, researchers have explored the potential of folate receptors and how their unique biology and function in the brain may result in more specialized and safe therapeutics.

Within the past two decades, folate receptors have risen to increased prominence among researchers because of one primary trait: expression. Folate receptors are expressed in a wide variety of epithelial cancers, ranging from breast cancer to brain cancer. 5 That said, cancer cells express folate receptors approximately 500 times more than corresponding healthy cells by comparison. 6 With this vast difference in expression in mind, folate receptors can be used as a biomarker for cancer therapy—signifying the presence of brain cancer—as well as a mechanism through which a drug-delivery pathway can be devised, bringing about targeted chemotherapeutic drugs. These same targeted drugs would resolve the aforementioned problem posed by anticancer drugs and ultimately give rise to less toxicity toward noncancer cells.

Running parallel to any study on receptors expressed on cancer cells is the unique and vast opportunity for nanoparticles to serve as chemotherapeutic agents. A wide variety of nanoparticle types have proved to be promising in treating cancer cells, ranging from the experimentally used gold nanoparticle to the clinically approved, albumin-based Abraxane. In this same vein, if researchers were able to synthesize a nanoparticle to operate in conjunction with the folate receptors expressed in brain cancer, the issue of damaging healthy cells would be eliminated by way of the receptor’s drug-binding delivery pathway.

In this Mini-Review, the structure and role of folate receptor in glioma will be briefly discussed followed by a short note on the folate-targeted nanoparticles used in glioma specifically. The biological nature of the folate receptor family will be addressed, as well as how the specific receptors operate within the body. Though the folate receptor as it behaves in cancer cells is of particular interest to researchers, the receptor plays a vital role in furthering the growth and health of noncancer cells in an unaffected organism. Then, the biotechnological potential of the folate receptor will be addressed, detailing both the synthesis of folate-receptor-specific nanoparticles and their current role in anticancer therapy. Moreover, distinct examples of folate-based drug delivery systems undergoing extensive research will be outlined in order to illustrate the positive impact these receptors may hold on the future of brain cancer theranostics. Thus, this Mini-Review serves to synthesize and make clear how folate receptors and their accompanying nanoparticle systems may serve as not just experimental research opportunities, but concrete therapy
options for the thousands of brain cancer patients in need of reliable and effective care.

**FOLATE RECEPTORS (FR)**

Folate receptors (FR) are the glycoprotein-based receptors in the 38–45 kDa molecular weight range. Folate receptors (FRα, FRβ, FRγ, and FRδ) are cysteine-rich cell-surface glycoproteins that bind folate with a high affinity to mediate cellular uptake of folate. They are of several isoforms such as FRα, FRβ, and FRγ. Of these, in the context of cancers, FRα and FRβ are of importance. FRα are overexpressed in many cancers such as brain tumors (about 90% expression) and cancers such as brain, ovarian, lung, and so on. Because of such high expression levels in cancer, FRα serves as a prognostic marker for cancers. FRβ is extensively seen on activated macrophages and has been used for targeting inflammatory diseases. Further, they are also found on the surface of immune cells responsible for tumor progression such as CD163+, CD68+, and IL-10-producing tumor-associated macrophages. This discovery has led to a great interest in its application for tumor therapy by way of reprogramming the immune responses.

**Structure of Folate Receptor.** Folate receptor alpha, or FRα, is a member of the folate receptor family that has a high affinity for folic acid, a necessary nutrient that can be converted by the body into folate and utilized during the synthesis of both DNA and RNA alike, as well as cell division. FRα has a globular structure stabilized by eight disulfide bonds and contains a deep open folate-binding pocket composed of residues that are conserved in all receptor subtypes. The folate pterate moiety is buried inside the receptor, whereas its glutamate moiety is solvent-exposed and exposed out of the pocket entrance, allowing it to be conjugated to drugs without adversely affecting FRα binding. The difference designating FRα from its fellow folate receptors does not emerge from its structure but rather from its location, as well as stage of human development (Figure 1). Of the three folate receptors, FRα is considered the “adult” receptor, with FRβ expressed in the placenta (though recently also detected in bone marrow, the spleen, and the thymus) and FRγ behaving as a secretory protein (Table 1).

**FRα AND GLIOMAS**

FRα is of particular interest due to its heightened over-expression in various epithelial cancers, most notably brain cancer. Numerous studies have pointed to FRα as it is expressed in cancer cells as a potential contributor to the development and growth of cancer cells themselves, particularly as a signaling molecule. Overexpression of FRα coincides with elevated STAT3 signaling, a transcription factor in humans, hence suggesting that FRα plays a role in the malignancy of cancer cells, as transcriptional regulation plays a role in the overexpression of the cell cycle. When activated in gliomas, FRα plays a similar role—on a scale 500 times that of the receptors expressed in noncancerous tissue. The receptors are expressed at high levels in numerous cancers to meet the folate demand of rapidly dividing cells under low folate conditions.

As mentioned earlier in this section, FRα is significantly upregulated in the cancers such as glioma. FRα has a major role in transporting the folic acid into the cells. Folic acid is responsible for the initiation and propagation of cancer by its role in the nucleotide synthesis (by providing methyl groups for DNA methylation), cell division, and proliferation in the cancerous cells and reduced tumor-suppression. This is a vicious circle—the more there is proliferation, the more there will be folate receptor expression to compensate for the growing demand for nucleotides and nutrition.

In reference to its chemotherapeutic potential, folic acid can easily penetrate solid tumor cells, and it is the primary molecule responsible for the synthesis of macromolecules referred to as folate conjugates. In addition to folic acid, folate conjugates are able to interact with folate receptors as ligands (Figure 2). Because of folic acid’s ability to readily undergo chemical conjugation with other molecules, folate acid can be paired with anticancer drugs, bind tightly to the FRα of a brain cancer cell, and be internalized by the cancer cell by way of endocytosis. Once it has entered the cancer cell, the folate conjugate is cleaved inside the endosome, allowing the drug to escape and exert its activity on the cell while the folate

| organ                           | FRα | FRβ | FRγ |
|---------------------------------|-----|-----|-----|
| brain                           | very high | low | very low |
| eye                             | low | moderate | very low |
| endocrine tissues               | very low | moderate | very low |
| lung                            | moderate | low | moderate |
| proximal digestive tract        | high | moderate | very low |
| gastrointestinal tract          | low | moderate | very low |
| liver and gallbladder           | very low | moderate | very low |
| pancreas                        | very low | low | low |
| kidney and urinary bladder      | moderate | moderate | low |
| male tissues                    | low | moderate | very low |
| female tissues                  | moderate | very high | low |
| muscle tissues                  | very low | moderate | low |
| adipose and soft tissue         | very low | very high | low |
| skin                            | very low | low | very low |
| bone marrow and lymphoid tissues| very low | moderate | moderate |
| Blood                           | very low | moderate | very high |

The protein expression was evidenced by three sources: UniProt protein existence (UniProt evidence); a Human Protein Atlas antibody- or RNA based score (HPA evidence); and evidence based on PeptideAtlas (MS evidence).

![Figure 1. Visual representation of FRα as it appears and expresses itself on epithelial cells’ surfaces.](image-url)
Folate receptors are key players in the process of cellular uptake of folate and its conjugates. Upon binding, folate receptors mediate endocytosis, a process that involves the internalization of folate-conjugated nanoparticles. This internalization is mediated by receptor-mediated endocytosis (RME), which is specific to folate receptors and allows for targeted delivery of drugs to cancer cells.

**Polymeric Nanoparticles.** Polymeric micelles are nanoparticles composed of copolymers, which can include both hydrophilic and hydrophobic regions. The hydrophilic regions provide solubility in aqueous environments, while the hydrophobic regions can encapsulate hydrophobic drugs. The amphiphilic nature of these polymers allows them to spontaneously associate into micelles, which can then encapsulate drugs and deliver them to targeted sites.

**Folic Acid.** Folic acid is a water-soluble vitamin that is primarily found in dark, leafy greens. It plays a crucial role in the synthesis of DNA and RNA, and is necessary for the normal development of bones, teeth, and muscles in the body. In the context of cancer therapy, folic acid can be conjugated to nanoparticles to target folate receptors on cancer cells, thus facilitating the uptake of these nanoparticles.

**Folate-Targeted Nanoparticles.** Temozolomide, a chemotherapeutic agent used for gliomas, is often combined with folate-targeted nanoparticles. By attaching folate molecules to the nanoparticles, targeting of folate receptors on cancer cells is enhanced, leading to improved cellular uptake and therapeutic efficacy.

**Drug Administration.** PLGA nanoparticles are often used to deliver drugs across the blood-brain barrier (BBB), which is a key obstacle in the treatment of brain tumors. PLGA nanoparticles can be modified with folate ligands to enhance their targeting capabilities, allowing for more effective drug delivery to gliomas.

**Conclusion.** The combination of folate-targeted nanoparticles and folic acid promotes targeted drug delivery to cancer cells, particularly gliomas. This approach not only increases the efficacy of therapeutic agents but also minimizes toxicity to healthy tissues.

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**Figure 2.** Diagram representing a tumor cell’s uptake of folate and folate conjugate, respectively. As illustrated, the folate conjugate makes contact with the folate receptor, is internalized by endocytosis, and is cleaved and activated within the cell while the folate receptor is recycled to the surface of the cell.

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**References:**

1. Zheng et al., Determined that biocompatible PLGA-lipid with folic acid hybrid nanoparticles, due to the folate-receptor mediated endocytosis, showed significantly higher uptake by folate-receptor-positive MCF-7 cells as compared with PLGA-lipid NPs without folate. The results signal that the FA-targeted decorated nanoparticles exhibit higher cytotoxicity in MCF-7 cells compared with nontargeted nanoparticles, making the lipid-polymer nanoparticles provide biocompatible nanocarriers for cancer targeting therapy.

2. In specific reference to gliomas, positive outcomes are a genuine possibility in regard to the drug delivery system based on polymer–lipid hybrid nanoparticles. This has been emphasized by research performed by Agrawal et al., in which researchers developed FA-modified polymer–lipid hybrid nanoparticles (PLNs) loaded with paclitaxel conjugated to cyclo-[Arg-Gly-Asp-D-Phe-Lys] (PtxR-FPLNs) for brain tumor chemotherapy. The prepared PLNs were designed to be efficiently transported across the BBB and afterward interact with integrin on the surface of glioma cells which highly express integrin.
Synthesizing all of this information, polymeric nanoparticles, when used in conjunction with the folate receptor, may deem promising in the fight against gliomas because of their ample transportation and biodegradable capabilities.

**Liposomal Nanoparticles.** Liposomes, with their excellent biocompatibility, biodegradability, and low toxicity, have become increasingly prominent candidates for anticancer efforts by way of nanoparticles. Specifically, polyethylene glycol (PEG)-related liposomal nanoparticles may be functionalized with molecular targeting ligands, such as folate and folic acid; thus, these nanoparticles can be used by researchers interested in exploiting overexpressed folate receptors in cancerous brain tissue.

In one study, glioma cell lines were treated with folate-doxorubicin liposomes, which later showed increased affinity for binding on glioma cell lines due to the overexpression of the folate receptors in glioma cells. Upon treatment with folate-doxorubicin liposomes, the glioma cell lines exhibited a slower rate of proliferation.29

In another study conducted by Man Li et al., a hydrazone-based acid-cleavable phospholipid liposome was fabricated to target folate receptors. To improve cell internalization and penetration through the BBB, paclitaxel-loaded liposomes were modified with tumor microenvironment-cleavable folic acid and a cell penetrating peptide, dNP2. This mechanism and the interactions between folic acid and the folate receptor led to the enhanced cellular uptake of the liposomes. When the folic acid-paclitaxel liposomes were injected intravenously in mice with glioma, there was an increased accumulation of the drug in the glioma cells and its antitumor effects were amplified. The very configuration of the nanoparticle itself enabled deep penetration of the liposomes into the tumor cells, increased the cytotoxicity of paclitaxel-loaded liposomes in glioma cells, and made the glioma cells more prone to go through apoptosis.30

Liposomes also possess a wide degree of variability and manipulability, primarily through surface decoration with receptor recognition ligands as a means of targeting specific receptors and biomarkers. In a study by Shmeeda et al., folate receptor directed nanotherapies were found to increase drug levels in malignant cells, though research failed to highlight how brain cells in particular behave under similar conditions.31

**Metallic Nanoparticles.** Metallic nanoparticles are highly efficient because of their low cytotoxicity, tunable size and shape, and stable attachment of ligands and molecules. Gold nanoparticles are biocompatible, have been used as drug carriers in various diseases, and have a high surface area to volume ratio; this allows for a high drug loading capacity and drug stability. These nanoparticles can also control the release of the drug with internal or external stimuli.32

In a study done by Samadian et al., it was shown that folate-conjugated gold nanoparticles, loaded with anticancer drugs, are promising for targeted cancer therapy. Folate targeting strategies combined with the property of gold nanoparticles to absorb light will allow only cancerous cells to be attacked, while leaving the healthy cells untouched. Gold nanoparticles are known to have toxic side effects toward normal tissues but modifying the surface of the nanoparticle with folic acid can increase the efficiency of the gold nanoparticles while simultaneously decreasing their adverse effects. This shows that the folate-conjugated gold nanoparticles, combined with the folate receptor, may play an important role in the treatment of glioma.33

On the other hand, though silver nanoparticles are championed for their broad-spectrum antibacterial activity, silver nanoparticles are stunted by their cytotoxicity and genotoxicity at higher concentrations.34 Though promising in other realms of anticancer efforts, such as in human breast cancer cells, little research has either confirmed or denied the efficacy of silver nanoparticles when coupled with the folate receptor.

Moving past precious metals, zinc oxide (ZnO) nanoparticles have also been used as a prospective tool against gliomas. Marfavi et al. conjugated ZnO nanoparticles with folic acid, allowing the nanoparticles to easily pass through the cell membrane, and applied them to glioblastoma multiform (GBM) U87MG cell lines. Following a period of 12 hours, the viability for U87MG cells showed a significant decrease, both at 1.25 and 2.5 mg/mL concentrations.35

With all of this in mind, metallic nanoparticles as a general tool in antglioma efforts still must be further investigated, but trial and experimentation have proven their prospective effectiveness.

**Macrophage-Targeting Nanoparticles.** Macrophage-targeting nanoparticles, which take advantage of macrophages loaded in the innate immune system, are macrophages loaded with nanoparticles. At the tumor site, macrophages carry out their routine behavior as if unloaded—secretion hydrolyzed proteases, interferons, and enzymes in order to stunt tumor growth—while simultaneously releasing nanoparticles to supplement the antitumor efforts.

Kurahara et al., examined the relationship between folate receptor B-expressing macrophages and metastasis in pancreatic cancer patients. High levels of FRB+ macrophages corresponded to a high incidence of hematogenous metastasis, leading researchers to believe that the FRB+ macrophages play a key role in the tumor microenvironment. This makes FRB+ macrophages a biomarker for metastasizing pancreatic cancer cells. Knowing this, targeting FRB+ macrophages may serve as a potential future form of immunotherapy, as doing so will directly prohibit tumor progression.13

O’Shannessy et al. conducted a similar study, in which researchers observed folate receptor beta’s expression of macrophages in specific epithelial cancers. With epithelial ovarian cancer (EOC) host to high expression of both folate receptor alpha and beta, respectively, the team elected to investigate the cell-specific expression in gynecologic tissue. The study found that folate receptor beta was expressed virtually exclusively in both M1 and M2 macrophages, possibly representing tumor associated macrophages (TAMs) in epithelial cancers.34

After discovering that folate receptor B was highly expressed on macrophages in both human glioblastomas and rat C6 gliomas, respectively, Nagai et al. injected immunotoxins in afflicted mice to observe the effects of macrophage targeting. The TAMs were significantly depleted and tumor growth was reduced, suggesting that immunotoxins targeting FRB+ expressing macrophages may greatly progress antiglioblastoma efforts.35

In one specific study conducted by Pang et al., M1 macrophages were utilized as drug-carriers because of their stronger phagocytic ability than that of other macrophages and natural tendency to implant themselves into tumor tissue; the phagocytic nature is important, primarily because more drug-loaded nanoparticles may be taken up and subsequently delivered to the tumor site than M0 macrophages.36

On the other hand, though silver nanoparticles are championed for their broad-spectrum antibacterial activity, silver nanoparticles are stunted by their cytotoxicity and genotoxicity at higher concentrations.34 Though promising in other realms of anticancer efforts, such as in human breast cancer cells, little research has either confirmed or denied the efficacy of silver nanoparticles when coupled with the folate receptor.
imaging also showed that the DOX-PLGA-nanoparticle loaded M1 macrophages had higher distribution than free nanoparticles at the brain tumor site. The results showed that M1-nanoparticles increased cell interactions in tumors and better facilitated the delivery of the nanoparticles in tumor tissues in the glioma model. M1 macrophages loaded with DOX-PLGA-NPs had a significantly greater effect against glioma cells; this was confirmed when the group of mice that were treated with M1-nanoparticles had the highest expression of caspase-3 when compared to other groups which did not receive the DOX-M1-NP treatment. Similarly, the M1-nanoparticles were observed to pose a greater cytotoxic effect on glioma tumor cells than free nanoparticles. The accumulation of the M1 nanoparticles was also far greater than that of regular nanoparticles in tumor tissue; this would allow for the nanoparticles to carry out a more profound effect against the proliferation and growth of tumor cells. If these M1-nanoparticles were functionalized ligands such as folate or folic acid, the folate receptor would act as a mediator to transport these nanoparticles inside cells and increase their antitumor effects.

**Theranostic Nanoparticles.** Folate-targeted nanoparticles have been put to use as multifunctional nanoparticles for therapy as well as imaging of the gliomas to track the progression of the tumor upon treatment. Several researchers have been working on developing such targeted theranostic nanoparticles. For instance, Cai et al. studied a dual targeted nanoparticle (with targeting ligands as folate and cRGD peptide) as a theranostic system that not only accumulated in the brain tumor but also supported image-guided tumor suppressive photothermal therapy.39 Though much is remaining to perfect the science of theranostic application of folate-targeted nanoparticles, there are several successful systems synthesized for other cancers such as ovarian and breast cancers that could guide the research in this field.2,8,40–44

**FUTURE OBJECTIVES**

Folate receptors have proven, in several studies, to be a good target for formulating delivery systems in different types of cancers. Their application has been successfully extended to glioma treatment on the basis of the fact that they are highly expressed in the brain for transport of nutrients across BBB as well as a functional moiety in DNA methylation of cancers. It can be clearly seen from the specific studies cited for glioma treatment that folate targeting is a rewarding strategy. However, it needs much work to be successful clinically in treating gliomas.

Though the potential of folate receptors and their respective nanoparticles is great in regard to their role in combating brain gliomas, actually experimenting with and testing the efficacy of the folate receptor brings about complications for researchers. To elaborate, calling back to folate targeting, researchers must determine throughout their studies whether or not a monovalent conjugate, or single-drug conjugate, is of better use than a multivalent drug conjugate (Figure 3).

Several studies, including those tested at the clinical level by biopharmaceutical company Endocyte, have demonstrated that monovalent studies can successfully deliver their drug payload to cells overexpressing FRα while simultaneously decreasing unwanted, off-target side effects.45,46 On the other hand, a variety of studies, such as the ones by Silpe et al. and Stella et al., have illustrated that a multivalent approach serves as a more advantageous system. The aforementioned studies noted that the principle idea of adding multiple folic acid molecules on the surface of the drug carrier strives to promote higher binding avidity and affinity to FRα than a monovalent folic acid delivery system.47,48

Looking to the future, it is suggested that researchers take into account these studies in order to best devise and design a drug delivery system that is not simply the most efficient nor the most complex, but one that is the most effective in addressing the needs of patients with gliomas. Nanomedicine and biotechnology alike allow researchers unique opportunities and avenues of care, yet they must always be conscious of the audience this line of research impacts, and it is imperative that researchers take this into consideration throughout each step of the process. It is only evident from the few studies reaching the clinical trials (NCT01700569, Phase 1) that it is no simple task.

**CONCLUSION**

As nanotechnology continues to play an increasingly prominent role in the ways in which researchers observe patient treatment and care, folate receptors and the nanoparticles available to exploit them have presented themselves as promising tools in the battle against gliomas. The overexpressed folate receptors on the surface of glioma cells can be tackled by a unique folate targeting approach, though a wide variety of nanoparticles and drug delivery systems are available for experimentation.

With researchers being familiar with the long and arduous research and trial processes, they likewise must be conscious of who specifically is affected by the successes and struggles of nanoparticles. In tackling these experimental routes, researchers are responsible for paving the way for not just new advancements in nanotechnology but improved quality of life for those afflicted by gliomas. In anticipating a long, complex road of experiments, researchers are able to better prepare themselves and celebrate the work they do because they are the early steps toward improving the world around them and the health of those who inhabit it.
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**Notes**

The authors declare no competing financial interest.

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