Chinese Medical Journal®

Research progress on platelets in glioma

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Abstract

Gliomas are the most common primary neuroepithelial tumors of the central nervous system in adults, of which glioblastoma is the deadliest subtype. Apart from the intrinsically indestructible characteristics of glioma (stem) cells, accumulating evidence suggests that the tumor microenvironment also plays a vital role in the refractoriness of glioblastoma. The primary functions of platelets are to stop bleeding and regulate thrombosis under physiological conditions. Furthermore, platelets are also active elements that participate in a variety of processes of tumor development, including tumor growth, invasion, and chemoresistance. Glioma cells recruit and activate resting platelets to become tumor-educated platelets (TEPs), which in turn can promote the proliferation, invasion, stemness, and chemoresistance of glioma cells. TEPs can be used to obtain genetic information about gliomas, which is helpful for early diagnosis and monitoring of therapeutic effects. Platelet membranes are intriguing biomimetic materials for developing efficacious drug carriers to enhance antiglioma activity. Herein, we review the recent research referring to the contribution of platelets to the malignant characteristics of gliomas and focusing on the molecular mechanisms mediating the interaction between TEPs and glioma (stem) cells, as well as present the challenges and opportunities in targeting platelets for glioma therapy.

Keywords: Glioma; Tumor-educated platelet; Interaction; Diagnosis; Biomimetic membrane

Introduction

Glioma is the most common primary malignant tumor of the central nervous system (CNS), and glioblastoma (GBM) has the most unfavorable prognosis.[1] Emerging studies suggest that the tumor microenvironment (TME) is a vital regulator of glioma development and progression, and a comprehensive understanding of the TME could facilitate the development of therapeutic regimens for deadly gliomas.[2] Platelets, numbering between 1–3 × 10^9/L, are the smallest anucleated cells in blood, and their main role is to stop bleeding and regulate thrombosis. Platelets are also involved in regulating the processes of various diseases, such as inflammation and cancer.[3] During the progression of tumors, platelets play a significant role in promoting malignant biological behaviors such as angiogenesis, metastasis, and chemotherapy resistance.[3,4] In addition, platelets interact with non-tumor cells in the TME, such as pericytes, fibroblasts, and immune cells, ultimately intervening in tumor progression.[5,6]

Regarding the role of platelet count in glioma prognosis, previous studies have reached contradictory results, which may be impacted by distinct therapeutic regimens.[7–9] Recently, immunohistochemical detection confirmed that increased platelet counts in tumors were negatively correlated with the prognosis of GBM patients,[10] and decreased perioperative platelet aggregation suggested a better clinical outcome in GBM patients.[11] Pathological angiogenesis is a vital process in tumor progression that promotes nutrient supply and tumor cell dissemination and results in an immunosuppressive TME.[12] Although platelet-released cytokines can promote both the proliferation and migration of GBM cells and endothelial cells *in vitro*, no same function of platelet-induced tumor growth or angiogenesis was found *in vivo*, which suggested that increased platelet counts may be a consequence of tumor recruitment. Vascular thromboembolism is associated with increased mortality in patients with tumor.[13,14] Compared with healthy donors and high-grade glioma patients with *IDH* mutations, patients with newly diagnosed GBM and *IDH*-wildtype high-grade gliomas had significantly greater blood platelet counts.[15,16] The reported mechanisms of platelet activation and aggregation in glioma tissues are associated with nucleoside

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000003282

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Chinese Medical Journal 2024;XX(XX)

Received: 10-01-2024; **Online:** 10-09-2024 **Edited by:** Xiangxiang Pan

triphosphate diphosphohydrolase-2 (NTPDase2) expression in glioma cells and the expression of podoplanin (PDPN) in tumor cells.[17,18]

Cancer stem cells (CSCs) have been observed in many solid tumors and leukemias, exhibiting the ability to undergo self-replication, resist chemotherapy and radiotherapy, and initiate the formation of new tumors.[19] Accumulating studies have demonstrated that CSCs can be used as biomarkers for predicting the prognosis and early detection of tumors. CSCs share the same phenotypic and functional characteristics as metastasis-initiating cells (MICs). It is now believed that traditional treatment can effectively kill tumor cells in a highly proliferative state, but a small number of CSCs may tenaciously survive, resulting in tumor recurrence or metastasis.[20] Many studies have confirmed that tumors expressing stem cell markers are closely related to a poorer prognosis following chemoradiotherapy.[19] Given the important role of CSCs in the process of tumorigenesis, they have been widely studied as potential tumor therapeutic targets.

Although great progress has been made concerning the role of platelets in diagnosing and treating gliomas, a comprehensive literature summary of the most recent developments in the interactions and mechanisms between platelets and gliomas is highly warranted. In this review, we aimed to explore potential molecular targets for platelet-based treatment of gliomas by comprehensively summarizing the interactions and associated mechanisms between platelets and glioma (stem) cells. First, the relationships between the platelet count and malignant characteristics of gliomas, such as tumor growth, invasion, and treatment resistance, are summarized. Then, we discuss the progress in utilizing platelets for diagnostic purposes. Finally, we summarize the researches focusing on the antitumor efficacy of platelet-targeted therapy and biomimetic platelet membrane-coated drug carrier systems.

Functional Roles of Platelets in Gliomas

Platelet in tumor growth

Platelets can enhance the proliferation and migration of both GBM cells and vascular endothelial cells. Platelet-derived factors also promoted neovascular sprouting and the formation of capillary-like structures *in vitro*.[13] However, *in vivo* experiments showed that tumor size, vascular density, and proliferation index were not associated with platelet counts, which suggested that platelets were not sufficient to regulate GBM growth *in vivo*.[13] Regarding the interaction between platelets and glioma stem cells (GSCs), Sloan *et al*[10] reported that platelets mainly converge in the pseudopalisade necrosis area of GBM tumors, which was consistent with the main residential areas of GSCs indicating that platelet location may be determined by GSCs. In addition, increased platelet counts are positively correlated with glioma growth and negatively associated with patient prognosis. It also revealed that GSCs can activate platelets by producing thrombin, and in turn, activated platelets promote the stemness and proliferation of GSCs. Thus, pharmacological inhibition of endogenous Factor X (FX) and thrombin in GSCs effectively delays glioma growth *in vivo*, suggesting that targeting GSC–platelet interactions may have potential therapeutic value.[10] Taken together, the functional role of platelets in enhancing glioma growth is still controversial. More comprehensive studies should be conducted to identify whether platelets can promote the growth of glioma.

Platelet in tumor invasion

Not all tumor cells can metastasize, but CSCs, which account for a tiny proportion of malignant cells, are considered the initiators of metastasis.[21] CSCs in the circulation can form complexes with platelets, which can activate platelets to secrete more tumor growth factor-β1 (TGF-β1) and can also inhibit the antitumor activity of natural killer (NK) cells by downregulating the expression of natural killer Group 2 member D (NKG2D).[22] In addition, the expression of tissue factor (TF) on CSCs, which mediates platelet aggregation, was greater than that on non-stem tumor cells, thus promoting the activation of the coagulation system to form more CSC-platelet complexes, enabling the platelets to better protect circulating CSCs.[22] Cluster of differentiation 133 positive ($CD133^+$) prostate CSCs showed a greater ability to adhere to platelets than $CD133^-$ tumor cells because $CD133^+$ tumor cells express a higher levels of prothrombin and C-X-C motif chemokine receptor 4 (CXCR4), which combines with stromal derived growth factor-1α (SDF-1α) expressed on platelets and subsequently stimulates the invasion of CSCs.[23] As gliomas have a potent ability to diffuse infiltration,[24] whether platelets can regulate the invasion of glioma cells and the specific mechanisms involved should be further elucidated carefully.

Platelet in tumor resistance

The recommended first-line concurrent chemotherapy for glioma patients is temozolomide (TMZ).[25] Unfortunately, the vast majority of GBM patients inevitably experience rapid tumor recurrence, which considerably reduces their survival time.[26] Accumulating evidence suggests that multiple endogenous and exogenous factors contribute to the resistance of glioma cells to TMZ,[27] and GSCs mediated TMZ resistance plays a crucial role in tumor recurrence and aggressive growth.[28] Platelets can enhance the therapeutic resistance of tumor cells through various mechanisms [Figure 1]. For example, tumor-educated platelet (TEP)-secreted TGF-β1 can promote chemoresistance of pancreatic tumor cells to cisplatin treatment by activating the mitogen-activated extracellular signal-regulated kinase (MEK)/ Extracellular signal-regulated kinase (ERK) and Phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT) signaling pathways.[29] Platelet secretion promotes the growth of ovarian tumor spheres, which express increased levels of the stem cell markers CD133 and aldehyde dehydrogenase (ALDH) and have enhanced cell viability and chemoresistance. Analysis of the components of the platelet releasate (PR) revealed that it contains a large number of growth factors, such as

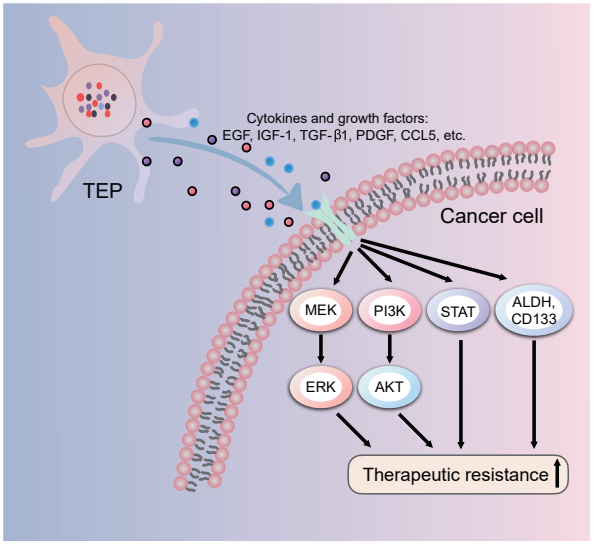

Figure 1: Mechanisms of TEPs promoting resistance of cancer cells. Resting platelets can be activated to transform into TEPs in the TME. TEPs enhance the therapeutic resistance of multiple cancers by secreting a variety of bioactive excretions, such as TGF-β, EGF, IGF-1, PDGF, and CCL5. Following the crosstalk of TEPs and cancer cells, several classical tumor-promoting signaling pathways in cancer cells are stimulated to mediate an increased survival of tumors. AKT: Protein kinase B; ALDH: Aldehyde dehydrogenase; CCL5: C-C motif chemokine ligand 5; CD133: Cluster of differentiation 133; EGF: Epidermal growth factor; ERK: Extracellular signal regulated kinase; IGF: Insulin like growth factor; MEK: Mitogen-activated extracellular signal-regulated kinase; PDGF: Platelet-derived growth factor; PI3K: Phosphoinositide 3-kinase; STAT: Signal transducer and activator of transcription; TGF-β1: Tumor growth factor-β1; TEP: Tumor-educated platelet; TME: Tumor microenvironment.

epidermal growth factor (EGF), platelet-derived growth factor (PDGF), TGF-β, insulin like growth factor (IGF), and C-C motif chemokine ligand 5 (CCL5) , which may mediate the protective effect on tumor cells by enhancing the stemness of tumor cells.[30] Inhibiting the interaction between cancer (stem) cells and platelets may be a potential strategy for improving tumor drug resistance. However, the effect of TEPs on the chemotherapeutic response of glioma (stem) cells remains unclear and has yet to be explored.

Platelets as Blood Biomarkers for Glioma Diagnosis and Treatment Monitoring

With the development of liquid biopsy technology, blood components, such as plasma, serum, extracellular vesicles, and circulating tumor cells, have been investigated for preoperative diagnosis and efficacy evaluation during cancer treatment.[31,32] Currently, the most common materials isolated for cancer detection include extracellular nucleic acids (cell-free DNA [cfDNA]), circulating tumor DNA (ctDNA), and circulating tumor cells (CTCs).[31] Detecting tumor-specific nucleic acid information helps clinicians predict diagnosis and prognosis, which provides the basis for selecting rational treatment regimens. In addition, postoperative monitoring contributes to evaluating therapeutic response and early detection of tumor recurrence. Although a variety of tumors harbor detectable ctDNA in the blood samples of patients according to analysis of a large number of point mutations and genomic rearrangements, ctDNA can be detected in less than 10% of glioma patients.[33] In addition, circulating glioma cells are considered feasible for glioma diagnosis, but their detection efficiency varies.[32]

Blood is rich in platelets, which are easy to separate and purify. Several studies have revealed the diagnostic value of platelets in gliomas. By comparing the RNA profiles of platelets in blood samples between glioma patients and healthy subjects, it was found that epidermal growth factor receptor variant III (EGFRvIII) could be detected in the platelets of 80% of GBM patients with *EGFRvIII* mutations, which could be attributed to platelets absorbing microcapsules containing mutated nucleic acid information released by GBM cells. However, this mutation could not be detected in low-grade gliomas because these gliomas do not contain the *EGFRvIII* mutation.[34] *In vivo* experiments showed that the expression of *EGFRvIII* could also be detected in the blood of platelets from nude mice in an orthotopic glioma model. This study suggested that the communication between glioma cells and platelets enables platelets to acquire genetic information about GBM. Therefore, platelets may serve as biomarkers for the early diagnosis of GBM.[34] In the process of platelets interacting with tumor cells, platelets are usually "educated" by tumor cells and then transformed into TEPs, which have underlying diagnostic value in various tumors.[35,36] As the spliced-RNA profiles of TEP in GBM patients have clearly changed, the RNA characteristics of TEP can be used to accurately distinguish GBM patients from asymptomatic healthy subjects with a detection accuracy of 95% and patients with neuroinflammation or other brain tumor diseases with a detection accuracy of 80% in a minimally invasive manner.[37] Apart from serving as fingerprints for GBM identification, the RNA profiles of GBM TEPs gradually decrease following tumor resection but increase when tumor progresses, and the accuracy of TEPs for therapeutic response evaluation reaches 85%, although further exploration with a larger sample size is needed.[37]

Early tumor detection benefits patients with more favorable survival due to the possibility of timely intervention in the early stage of tumor development. To this end, a new study developed a highly specific tumor diagnostic model by analyzing RNA sequencing data of TEPs from 18 different tumors, which was able to correctly determine the tissue origin of 5 tumors with 80% accuracy, including primary gliomas.[38] This study revealed that the platelet count is capable of accurately detecting early-stage tumors and could be a supplemental biomarker for blood-based cancer screening. α-granules represent the most abundant secretory granules in platelets and are diversely distributed under different health conditions.[39] Another recent study innovatively took advantage of structured illumination superresolution fluorescence microscopy to detect the subcellular structures of superresolution images of platelets for diagnosing multiple kinds of tumors, including 8 low-grade gliomas, 8 GBMs, and cervical, endometrial, and ovarian cancers.[39] The results revealed that the nanoscale distribution patterns of α-granules in the platelets of both low-grade gliomas and GBMs were scattered, with 30 or more dots in each platelet, which was 7 times greater than that in healthy donors, suggesting

that the patterns of α-granules were sufficient to serve as diagnostic biomarkers for the tumors mentioned above.[39] Moreover, α-granules in platelets also showed the potential to monitor the therapeutic response of tumors receiving treatment, with an area under curve (AUC) of 91.7%.

A comparison of the platelet counts of glioma patients before surgery and at 6 weeks after surgery revealed that decreased platelet levels during postoperative treatment are correlated with improved survival, which indicates that platelet counts can be used to evaluate the efficacy of treatment.[40] The survival of patients with recurrent GBM has always been inferior. Therefore, exploring factors that can predict treatment benefits in patients with relapse is important for clinical decision-making. A clinical study demonstrated that platelet counts correlated with the therapeutic response of recurrent GBM patients to bevacizumab.[41] Patients with recurrent gliomas had high platelet counts before bevacizumab treatment. Magnetic resonance imaging (MRI) suggested tumor shrinkage (indicating that treatment was effective), and the platelet level of patients decreased markedly compared with that at baseline. In contrast, the platelet counts increased again as the tumor progressed.[41] Although the alteration of platelet counts during glioma progression has predictive value for the prognosis of glioma patients, the clinical application of platelets for glioma diagnosis needs to be further explored. We summarized studies using platelet detection for glioma diagnosis in Table 1. Overall, TEPs have exciting potential for detecting early gliomas and appraising therapeutic responses during treatment [Figure 2].

Platelet-based Glioma Treatment

Targeting platelet–tumor cell interactions for glioma treatment

Glioma causes thrombocytosis in circulation and promotes the aggregation of platelets in tumors, which increases the risk of venous thrombosis and promotes malignant features, such as tumor proliferation. Due to the close interaction between platelets and glioma (stem) cells, accumulating studies are trying to develop new therapeutic regimens for intractable GBM based on platelets. Although hypercoagulation is an unfavorable predictor for cancer patients,[14,42] a retrospective study revealed no correlation between anticoagulant use and better outcomes in patients with GBM, and anticoagulant therapy was associated with a worse prognosis for patients with GBM, which may be due to the retrospective nature and small cohort of this study.[43] The anti-platelet drugs induced functional deficiency of platelets in tumor patients, which may be consistent to the myelosuppression exerted by chemotherapy. For example, lomustine has been considered a salvage treatment for recurrent GBM and usually causes thrombocytopenia, which inevitably limits adequate drug exposure and may be associated with inferior progression-free survival.[44] Moreover, clinicians need to pay attention to lethal bleeding caused by antiplatelet drugs. The survival of GBM patients may not benefit from anticoagulation therapy. Therefore, platelet-targeted tumor therapy without impairing the physiological functions of platelets deserves further investigation.

Cessation of the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab is usually followed by a rebound in tumor growth,[45,46] which is ascribed to rapid tumor vascular regrowth and enhanced ovarian cancer cell proliferation.[47] In addition, increased platelet aggregation has also been found in tumors after the withdrawal of antiangiogenic drugs, whereas tumors with little platelet infiltration exhibit a delayed growth rate.[46] Mechanistically, focal adhesion kinase (FAK) expressed in platelets regulates platelet migration into the TME, and the use of FAK inhibitors and antiangiogenic drugs can not only effectively inhibit tumor growth but also alleviate therapeutic effects after antiangiogenic agent withdrawal.[46] Thus, FAK may be a vital molecule involved in platelet aggregation after antiangiogenic agents are terminated. Synergistic blockade of FAK and VEGF may be beneficial for preventing tumor rebound. Recombinant anti-PDPN (NZ-1) immunotoxin inhibited the growth of GBM

Table 1: Studies focusing on platelet detection for glioma diagnosis.

Detection contents	Patient cohorts	Effect on diagnosis	References
Platelet counts	Recurrent GBMs treated with bevacizumab	Changes in platelet counts can predict the radiographic response of bevacizumab	[41]
Platelet counts	Primary GBMs treated with the Stupp protocol	Platelet decreasing from baseline to week 6 was a longer survival predictor	[40]
α-granules in platelets	Gliomas	α-granules imaged by superresolution fluorescence microscopy have the potential to diagnose gliomas	[39]
Mutant *EGFRvIII* in platelets	Gliomas	Blood platelets containing *EGFRvIII* RNA in glioma patients	[34]
TEP mRNA	Pan-cancer including GBMs	TEP mRNA profiles are valuable for blood-based cancer diagnosis	[35]
Spliced RNA profile of TEPs	Brain tumors including GBMs	TEPs have the potential to diagnose and monitor the progression of GBM patients	[37]
TEP-derived RNA	Pan-cancer including gliomas	TEP RNA-based blood tests enable the diagnosis of 18 cancer types	[38]

EGFRvIII: Epidermal growth factor receptor variant III; GBM: Glioblastoma; mRNA: Messenger RNA; TEPs: Tumor-educated platelets.

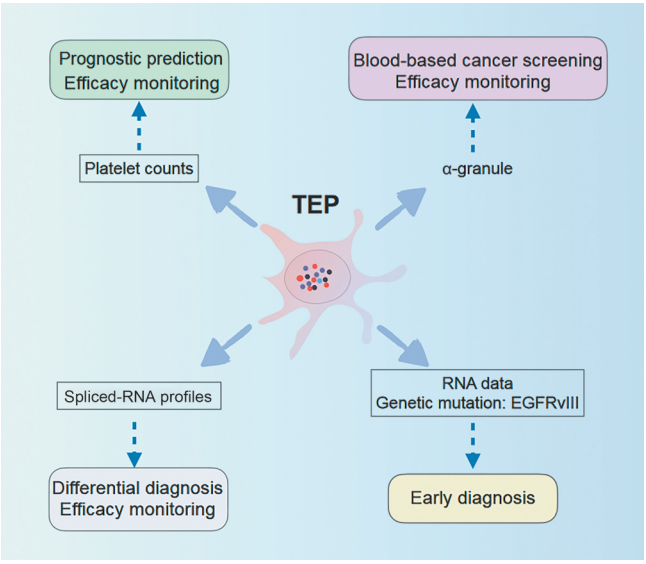

Figure 2: Platelet contents are used for glioma detection. Platelet counts can indicate the prognosis of glioma patients and the effectiveness of therapeutic regimes for recurrent GBMs. The components of TEPs, such as distribution patterns of α-granules, genetic mutations, and RNA profiles show great potential for early diagnosis of gliomas and therapeutic efficacy monitoring, thus providing a practical reference for clinical treatment. EGFRvIII: Epidermal growth factor receptor variant III; GBM: Glioblastoma; TEP: Tumor-educated platelet.

cells and increased the survival of tumor model mice in preclinical *in vitro* and *in vivo* experiments, whereas the study did not show the effect of the immunotoxin on platelet accumulation or aggregation in a tumor model.[48] Another study demonstrated that anti-PDPN neutralizing antibodies could reduce the proliferation and invasion of GBM cells. In addition, blocking PDPN also decreased platelet and GBM cell aggregation.[49] These findings suggest that the PDPN protein expressed on glioma cells is involved in the malignant behaviors of gliomas, which makes it an intriguing therapeutic target. An antagonist of the P2Y(12) receptor in platelets not only delays glioma growth by inhibiting platelet activation[43] but also eliminates the proliferation and invasion of GBM cells and leads to tumor autophagy through direct contact with the P2Y(12) receptor in tumor cells.[50] Li *et al*[51] genetically modified platelets to express surface-bound tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and the TRAIL-positive platelets were sufficient to kill cancer cells *in vitro* and inhibit the formation of metastases in mouse models. Taken together, these findings suggest that targeted therapies based on blocking platelet–tumor (stem) cell interactions may be an effective way to eliminate gliomas and can also prevent complications caused by disorders in platelet function.

Platelet-derived drug carriers in glioma treatment

As CSCs commonly exhibit increased therapeutic resistance, emerging evidence suggests that targeting CSCs is a more rational method for preventing malignant tumors.[52] Photothermal therapy (PTT) utilizes photosensitive nanoparticle-mediated light-to-heat transformation to effectively shrink tumor tissues and is a promising approach for cancer treatment.[53] Among all photothermal nanoparticles, Food and Drug Administration (FDA)-approved iron oxide nanoparticles (Fe_3O_4) have been widely used in PTT.[54] However, due to their nonspecific targeting ability and rapid clearance of intruding iron oxide nanoparticles by the innate immune system, nanoparticles are limited from accumulating in tumors, which inevitably weakens the antitumor therapeutic effect of PTT. In addition, the blood–brain barrier (BBB) is also one of the reasons why numerous anticancer drugs have lost their optimal antitumor activity in gliomas.[55]

In recent years, biomimetic cell membrane-coated drug carrier systems have attracted great attention because of their excellent biocompatibility and efficiency.[56] Previous studies reported that nanoparticles coated with biomimetic cell membranes, such as membranes of red blood cells, white blood cells, stem cells, and platelets, could prolong the time that nanoparticles accumulate in tumors.[57,58] The mechanisms of platelet-targeted therapy depend on the strong binding of platelet membrane-coated nanoparticles to the CD62p and CD44 receptors on tumor cells.[59] In addition, the local disruption of the BBB caused by glioma excision exposes the extracellular matrix, which promotes the aggregation of a large number of platelets at the surgical margin.[60] A study reported that platelet membrane-coated photothermal nanoparticles showed good antitumor activity in an immunocompetent combination of *Tgfbr1* and *Pten* conditional knockout head and neck squamous cell carcinoma (HNSCC) mouse model.[61] While this therapeutic approach was unable to effectively target CSCs in the TME, and tumor progression eventually occurred. Further experiments showed that a hybrid cell membrane PTT significantly enhanced tumor elimination capability by constructing fused CSC-platelet membrane-coated Fe_3O_4 nanoparticles ([CSC-P]MNs).[62] The enhanced antitumor activity was attributed to the use of both platelet membranes, which confer the ability of immune evasion to nanoparticles, and CSC membranes, which contain specific surface adhesion molecules that help to target CSCs. Although PTTs have been investigated for the treatment of gliomas,[63,64] studies investigating the efficacy of biomimetic cell membrane-coated PTTs in glioma therapy are relatively rare.[65] A natural and less toxic β-mangostin extract inhibited glioma growth by inducing oxidative damage through the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway.[66] The poor tumor cell targeting ability and poor permeability of the BBB of β-mangostin have limited its application in tumor treatment. Therefore, Wu *et al*[67] synthesized β-mangosteen-loaded platelet-C6 glioma cell hybrid biomimetic membrane-camouflaged NPs (β-PCNPs) for targeting gliomas, which exhibited enhanced tumor targeting properties and excellent antitumor activity. *In vitro* studies also showed that platelets could also be used as transporters to efficiently transfer cytotoxic quercetin into GBM cells, enhancing the antitumor effect of quercetin on glioma cells.[68]

Thrombus formation followed by vascular endothelium damage is a rapid physiological process of blocking blood leakage from damaged vessels.[69] This rapid process inevitably decreases the efficacy of transporting biomimetic platelet nanodrugs across the BBB and limits the full

antitumor potential of these nanodrugs.[59] To resolve this urgent challenge of rapid thrombus formation-induced lower efficiency of biomimetic platelet nanodrugs, the latest research illustrated that preoperative administration of platelet membrane-coated heparin-based doxorubicin (PM-HDOX) significantly enhanced BBB transmission and surgical margin-targeted efficacy for xenograft GBM and inhibited the growth of postoperative residual tumors in mice.[70] These findings demonstrated that platelet membranes could be used as a basic system to construct biomimetic carriers for effectively transporting anticancer drugs, but the administration window should be considered to improve the targeting accuracy and efficacy of glioma treatment.

Studies have shown that photodynamic therapy (PDT), which can target tumor cells and is highly safe, can effectively inhibit tumor growth, and photosensitizers are a key element of PDT.[71] To maximize the therapeutic effect of PDT for gliomas, new approaches to surmount defects in photosensitizers, such as poor tumor targeting, weak tissue penetration of excitation light, and a short plasma half-life, are needed. In a recent study, a photosensitizer was rapidly and accurately transported to GBM cells in an intracranial nude mouse model using photosensitizer-loaded platelets (BNPD-Ce6@Plt), which effectively inhibited intracranial tumor growth via increased reactive oxygen species (ROS) generation and DNA damage, reduced viability, and promoted tumor cell death. In addition, the study did not show significant side effects on the critical organs of the animals.[72] This study provided compelling evidence that platelets can efficiently carry nanophotosensitizers to gliomas to achieve highly targeted and efficacious PDT. Sonodynamic therapy (SDT) depends on a sonosensitizer with selective tumor accumulation to destroy tumor cells under ultrasound irradiation (UI).[73] To overcome the difficulty of distributing and accumulating sonosensitizers in tumor tissues, the effects of ultrasound-triggered release and tumor chemotaxis on SDT should be investigated. Wang *et al*[74] designed a new nanoformed sonosensitizer that consisted of iron oxide nanoparticles coated with polyglycerol and doxorubicin and loaded with chlorine e6 (IOPD-Ce6) and loaded IOPD-Ce6 with platelets, which exhibited a pronounced ability to result in cell death and suppressed intracranial GBM growth *in vivo*. This evidence suggests that platelets are reliable for transferring sonosensitizers into the GBM in an ultrasound-triggered manner and subsequently mediating the antitumor activity of SDT.

It is well known that macrophages polarizing to the M2 type are tightly associated with an immunosuppressive TME in GBM[75] and participate in suppressing the infiltration and function of T cells, both directly enhancing immune evasion and immunotherapy resistance of tumor cells.[76] Biomimetic drug carriers constructed from platelet membranes show potential for potent inhibition of tumor-associated macrophages (TAMs) to promote immunotherapy sensitivity. Quickly proliferating cancer cells produce increased lactate in the hypoxic microenvironment, which is reported to promote immune escape by polarizing TAMs to M2 macrophages and suppressing the immunocompetence of $CD8^+$ T cells,[77] suggesting that lactate is a potential immunotherapeutic target. Recent research constructed a biomimetic nanosystem combining metal-organic frameworks coated with platelet membranes for tumor-specific targeting and lactate oxidase (Lox) and oxaliplatin (Oxa) for cancer treatment, which exhibited encouraging antitumor efficacy via abundant accumulation of the nanosystem in tumors. Mechanistically, these nanoparticles induced the potent consumption of lactate, increased the infiltration of cytotoxic T cells and M1 macrophages in tumors, and decreased the infiltration of regulatory T cells (Tregs).[78] Another biomimetic photothermal nanosystem of Au@Fe-PM with increased tumor-targeting capacity constructed from an Au nanorod-coated ferric hydroxide and platelet membrane significantly promoted the antitumor immunity of PTT. Interestingly, the ferric hydroxide in Au@Fe-PM can repolarize M2 macrophages into M1 macrophages via *P38*- and *STAT1*-mediated molecular pathways. In addition, $CD8^+$ T cells are also significantly recruited to the TME to potentiate antitumor immunity through elevated secretion of the proinflammatory cytokines tumor necrosis factor (TNF-α) and interleukin-6 (IL-6).[79] Moreover, an integrated cancer treatment strategy combining inhibition of TAMs and immune checkpoints enhances the immunotherapeutic response by prolonging tumor relapse. One study designed alginate-based hydrogels modified with pexidartinib (PLX)-loaded nanoparticles (PLX-NPs) to persistently inhibit TAM functions and created anti-PD-1-conjugated platelets (P-aPD-1) to achieve tumor-specific recruitment and reactivation of T cells.[80] These inspiring results suggest that targeting TAM-induced amelioration of tumor immunosuppression aided by platelet-biomimetic membranes can collaboratively improve immunotherapeutic efficacy, thus preventing rapid recurrence even in cold immune tumors. Table 2 summarizes therapeutic approaches for gliomas and other tumors that involve the use of platelets.

Challenge and Perspective

It is well known that cancer cell-centric therapeutic strategies to date have barely eradicated all tumor cells. Moreover, the TME, which contains multiple non-tumor cells and biological factors, also controls the progression of malignancies by regulating tumor proliferation, invasion, metastasis, therapeutic resistance, etc.[4] This review focuses on the vital role of platelets in the prognosis, malignant characteristics, diagnosis, and targeted therapy of gliomas [Figure 3].

First, perioperative platelet counts can be a critical reference index for helping clinicians design appropriate therapeutic and follow-up regimens for high-risk patients. Therefore, larger analyses and pooling data from several centers investigating the association between platelet counts and the progression of gliomas may be worth exploring in future studies. Regarding the relationship between platelets and glioma cells, glioma cells can recruit platelets from the circulation into glioma tissues and educate them to become TEPs. TEPs play a role in mediating abnormal angiogenesis, tumor invasion, and chemoresistance in gliomas and are promising biomaterials for glioma-targeted therapy.

Table 2: Summary of platelet-based treatment of tumor.

Drug name	Tumor category	Research phase	Target or structure	Mechanism	Outcome	Reference
Heparin, Factor Xa inhibitor, and vitamin K antagonists	GBM	Clinical trail	Anticoagulants	Unknown	Do not improve overall survival	[43]
GSK2256098	Ovarian cancer	Preclinical mice	FAK	Preventing platelets aggregating in tumors after withdrawing antiangiogenic agents	Tumor rebound inhibition	[46]
NZ-1-(scdsFv)-PE38K-DEL	GBM and medulloblastoma	Preclinical mice	PDPN	Unknown	Promoting mice survival	[48]
Monoclonal antibody (NZ-1.3)	U87MG cells	*In vitro*	PDPN	Reducing tumor cell viability and invasion, inhibiting tumor cell-platelet aggregation	Tumor inhibition	[49]
Ticagrelor	GBM cells	*In vitro*	P2Y12 receptor	Decreasing proliferation and migration, and leading to autophagy of GBM cells	Tumor inhibition	[50]
TRAIL-expressing platelets	CTCs	Preclinical mice	TRAIL	Inducing cell apoptosis *in vitro* and reducing metastases	Attenuating metastases	[51]
BLIPO-1048	C6 glioma cells	Preclinical mice	PM-camouflaged nanoprobes	Escaping phagocytosis by macrophages and binding to CD 44 on cancer cells, leading to cell apoptosis	Tumor inhibition	[65]
β-PCNPs	C6 glioma cells	Preclinical mice	Platelet and tumor cell membrane camouflaged β-mangostin-loaded NPs	Improved targeting efficiency and leading to cell apoptosis	Tumor inhibition	[67]
Quercetin-loaded platelet	U373-MG	*In vitro*	PM as drug carrier	Platelet is an effective drug carrier	Unknown	[68]
PM-HDOX	GBM resection models	Preclinical mice	Postoperative thrombus attached to the damaged blood vessels	Enhanced BBB-crossing and surgical margin-targeted efficacy	Residual tumor inhibition	[70]
BNPD-Ce6@Plt	GL261	Preclinical mice	Platelet-loaded with Ce6	Increased ROS generation and DNA damage, reduced viability, and promoted cell death	Highly targeted tumor inhibition	[72]
IOPD-Ce6@Plt	GBM	Preclinical mice	Platelets with ultrasound-triggered release property	Increased ROS production, DNA injury, viability loss, and cell death	Highly effective SDT of GBM	[74]
PMOL	4T1 cells	Preclinical mice	Lox	Increased lactate consumption, infiltration of cytotoxic T-cells, and M1 Macrophages	Enhancing antitumor immunity	[78]
Au@Fe-PM	4T1 cells	Preclinical mice	M2 TAMs	Repolarization of M2 TAMs to M1 TAMs	Enhancing antitumor immunity	[79]
PLX-NP-P-aPD-1@Gel	B16F10 cells, CT26 cells, and 4T1 cells	Preclinical mice	CSFR and PD1	Blocking CSFR for TAM depletion and anti-PD1	Enhancing anti-PD1 efficacy	[80]

Au@Fe-PM: Iron-based second near-infrared (NIR-II) photothermal nanoplatform; BBB: Blood–brain barrier; BLIPO-1048: Platelet membrane-embedded IR 1048; BNPD-Ce6@Plt: Chlorine e6 (Ce6) loaded to boron nitride nanoparticle; CSFR: Colony-stimulating factor 1 receptor; CTC: Circulating tumor cell (triple-negative breast cancer and prostate cancer cells); FAK: Focal adhesion kinase; GBM: Glioblastoma; GL261: Mouse glioma 261; IOPD-Ce6: Iron oxide nanoparticles coated with polyglycerol and doxorubicin and loaded with chlorine e6; Lox: Lactate oxidase; NP: Nanoparticle; OL: Oxaliplatin; P-aPD-1: Anti-PD-1-conjugated platelets; β-PCNPs: Platelet and tumor cell membrane camouflaged β-mangostin-loaded NP; PD1: Programmed death1; PDPN: Podoplanin; PLX: Pexidartinib; PMOL: Platelet membrane coated OL and Lox; PM-HDOX: Platelet membrane-coated doxorubicin; ROS: Reactive oxygen species; SDT: Sonodynamic therapy; TAM: Tumor-associated macrophage; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand U373-MG is the human glioma cell line. GL261 is the murine glioma cells. 4T1 cells are 6-thioguanine (6-TG)–resistant murine MBC cells. B16F10 is a cell line derived from skin tissue of a mouse with melanoma. CT26 is an N-nitroso-N-methylurethane-(NNMU) induced, undifferentiated colon carcinoma cell line.

Accumulating evidence suggests that the interaction between platelets and tumor cells is the key element mediating tumor progression and is an intriguing target for intervening in tumor development without dampening the essential biological function of platelets. However, there is little research on the interaction between GBM cells and platelets, let alone on platelet-targeted therapies, and extensive *in vitro* and *in vivo* experimental investigations are needed. Despite accumulating experimental evidence suggesting that platelet-GBM cell interactions and platelet

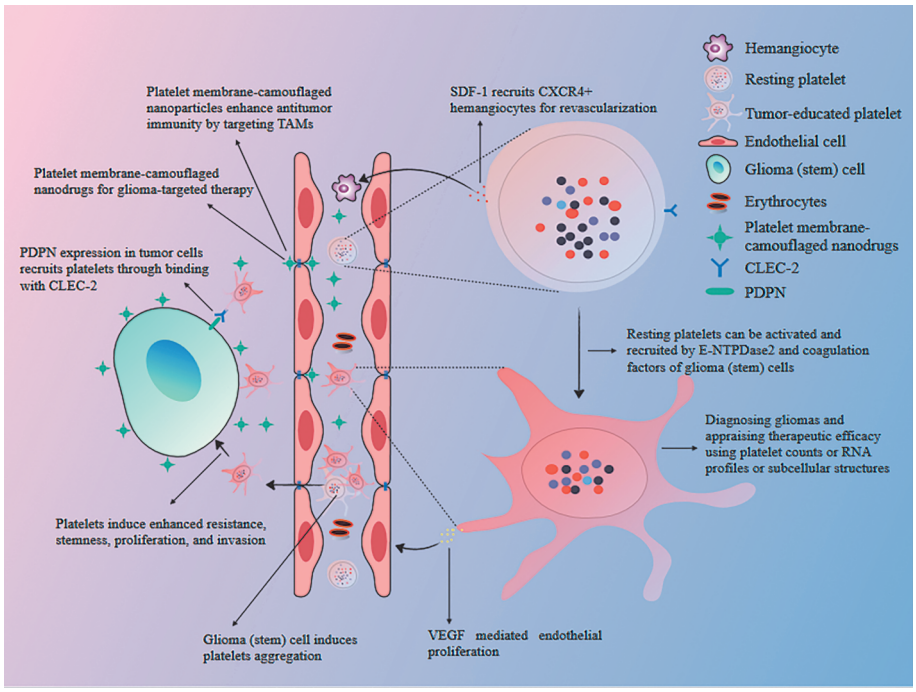

Figure 3: Current perspectives of platelet in the management of glioma. Glioma (stem) cells recruit more platelets into the TME and further activate them to be the TEPs. In turn, the interaction of the TEPs and glioma (stem) cells can promote the proliferation, invasion, stemness, and chemoresistance of tumor cells by forming a platelet-tumor cell complex or factors secreted by the TEPs. Platelets can capture the genetic materials released by glioma cells, which is helpful for early diagnosis of tumors, monitoring of therapeutic effects, and judgment of prognosis. Moreover, platelet membranes are attractive biomimetic materials for developing highly efficacious drug carriers to enhance the antitumor activity of multiple classical drugs. Platelet-targeted therapies based on the interaction between platelets and glioma cells are also a potential approach to overcome the malignant progression of gliomas. CLEC-2: C-type lectin receptor type 2; CXCR-4: Chemokine receptor 4; E-NTPDase2: Ectonucleoside triphosphate diphosphohydrolase2; PDPN: Podoplanin; SDF-1: Stromal derived growth factor-1; TAM: Tumor-associated macrophages; TEPs: Tumor-educated platelets; TME: Tumor microenvironment.

membranes could be used as biomimetic materials to enhance the therapeutic response against GBM. However, we acknowledge an enormous gap in translating fundamental research from the laboratory bench to the bedside. Emerging evidence indicates that tumor organoids are a valuable platform for recapitulating parent tumors and are appropriate for testing therapeutic agents in preclinical studies.[81] Thus, extensive future research targeting platelets for GBM therapy should be conducted that utilize more advanced platforms to achieve the greatest possible transformation.

Funding

This study was supported by the Sichuan Science and Technology Program (Grant No. 2023YFQ0002 to Yanhui Liu), the internal research funds in West China Hospital of Sichuan University (Grant No. 19HXCX009 to Yanhui Liu), and the Medical Science and Technology Project of Sichuan Health Commission (Grant No. 21PJ033 to Yanhui Liu).

Conflicts of interest

None.

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How to cite this article: Zuo MR, Li TF, Wang ZH, Xiang YF, Chen SL, Liu YH. Research progress on platelets in glioma. Chin Med J 2024;XXX:1–10. doi: 10.1097/CM9.0000000000003282