J Cancer Immunol. 2025;7(3):123–127.

Journal of Cancer Immunology Commentary

Blood Clotting Contributes to a Malignant Glioma Phenotype: A Commentary

Lynn M. Knowles[1], Tamara C. Kiwitt[2], Jan Pilch[2,*]

[1]Institute of Clinical Hemostaseology and Transfusion Medicine, Saarland University and University Medical Center, Homburg/Saar, Germany

[2]Institute for Transfusion Medicine and Hemostasis, University Hospital Augsburg, Augsburg, Germany

[*]Correspondence should be addressed to Jan Pilch, jan.pilch@uk-augsburg.de

Received date: June 03, 2025, **Accepted date:** August 12, 2025

Citation: Knowles LM, Kiwitt TC, Pilch J. Blood Clotting Contributes to a Malignant Glioma Phenotype: A Commentary. J Cancer Immunol. 2025;7(3):123–127.

Invasive Properties of Glioma Cells are Critical to their Malignant Phenotype

High-grade gliomas are malignant brain tumors that are derived from glial progenitors, oligodendrocytes or astrocytes [1]. The prognosis of malignant glioma is poor with an overall survival of 12-15 months for glioblastoma (GBM) and 2-5 years for anaplastic glioma. A hallmark of glioma is the diffuse infiltration of the neuropil, which regularly prevents complete surgical removal even in premalignant lesions [2]. While gliomas are generally considered to be non-metastatic, they are able to activate transcriptional programs known to promote mesenchymal cell functions that are associated with increased tumor cell invasion, a high rate of proliferation and poor patient survival [3]. Therefore, tumor cell invasion is a major aspect of glioma pathogenicity and defining the underlying adhesive mechanisms could lead the way to reversing the diffuse growth pattern of this malignancy.

The basic components of the brain extracellular matrix (ECM) are hyaluronan, chondroitin sulfate proteoglycans, and tenascin-R. Together, they form a 3-dimensional (3D) scaffold that promotes neurite outgrowth and prevents infiltration of both inflammatory and tumor cells [4]. Invasion into the interstitial spaces of the brain becomes possible after upregulation of CD44 in glioma cells, which takes place early during gliomagenesis and promotes glioma invasion into the neuropil through interaction with its ligand hyaluronan [5]. As gliomas progress, they begin to overexpress integrins and fibrillar ECM proteins such as fibronectin, collagen, and laminin. Binding of these ECM proteins to their complementary integrin receptors on glioma cells contributes to intracellular signals in support of glioma cell migration, growth, and survival [6–9]. These processes are clinically relevant because overexpression of ECM proteins and their integrin binding partners in glioma tissue correlates with decreased survival of patients afflicted with glioma [10,11]. Binding of integrins to their ligands in the ECM is instrumental for glioma infiltration alongside the basement membrane of the brain vasculature as well as neuronal, astrocyte, or white matter tracks [6,12]. In addition, cell adhesion plays an important role for glioma stem cells (GSC), which can be maintained through binding of glioma integrins α6 and α7 to laminin in perivascular niches of the brain [13,14]. Other functionally relevant integrins on GSCs include integrins αvβ3, αvβ5, αvβ8, and α2β1, suggesting that targeting adhesive interactions of glioma cells with their respective extracellular matrix could have a significant impact on controlling infiltration and growth of glial brain tumor cells [10,15–17].

Blood Clotting Represents a Relevant Modification of the Glioma Extracellular Matrix

The diffuse growth pattern of high-grade glioma is contingent on adhesive interactions of integrins with fibrous glycoproteins that are not present in the normal brain [18]. Therefore, glioma growth depends on the *de-novo* expression of polymeric glycoproteins such as tenascin-C, fibronectin, collagen, and laminin by tumor, stromal, and endothelial cells [7,12,19,20]. An alternative mode of brain tissue remodeling results from circulating adhesion proteins such as fibrinogen, plasma fibronectin, and vitronectin that extravasate together

with plasmatic coagulation factors and become incorporated into a provisional fibrin matrix [21–23]. This process is caused by a general procoagulant shift in glioma tissue that leads to thrombotic occlusion of tumor blood vessels and subsequent extravascular clotting in tissue voids generated by ischemic tumor cell necrosis [24,25]. The driving force behind the procoagulant shift in high grade gliomas is the overexpression of tissue factor, which is further enhanced by the hypoxic conditions in areas of tumor ischemia [24]. Hypoxia is also a strong inducer of VEGF, which leads to the formation of a hyperplastic and distorted vasculature that is unable to maintain a directed blood flow [26,27]. Accordingly, VEGF has been found to be upregulated in blood samples of glioma patients [28]. The resulting state of hypercoagulability is particularly prominent in patients with high-grade glioma and glioblastoma as their course of disease is frequently complicated by the occurrence of venous thromboembolism (VTE) [29]. VTE in glioblastoma patients often coincides with thrombotic occlusion of the tumor vasculature and the development of tumor cell necrosis [30,31]. This provides the functional basis for the large deposits of fibrin that can be found in tumor tissue of patients with glioblastoma and, to a lesser extent, in patients with astrocytoma grade 2 and 3 [32]. Normal brain, on the other hand, is essentially free of fibrin suggesting that the presence of fibrin in the tumor interstitial spaces is a specific modification of the extracellular matrix of malignant brain tumors.

Blood Clotting and Subsequent Fibrin Degradation Promote Glioma Growth

Overexpression of procoagulant factors in glioma is clinically relevant as there is a strong inverse relationship between the survival of glioma patients and the extent of necrosis and clotting in the corresponding tumor tissues [30,33]. Mutant IDH1, on the other hand, confers potent anti-thrombotic properties and, therefore, protects patients with IDH1-mutated gliomas from intratumoral thrombosis and subsequent tumor necrosis resulting in a significantly improved outcome [33]. Notably, mutant IDH1 not only inhibits tumor thrombosis locally but also lowers the incidence of paraneoplastic VTE systemically. This finding was confirmed in a prospective cohort study where the combination of IDH1 mutation status with the prothrombotic factor podoplanin could help to predict the VTE risk in glioma patients [34]. The implication of these studies is that it may be possible to identify glioma patients with a high risk of VTE and, conversely, reduce the risk of hemorrhagic stroke due to thromboprophylaxis in patients with a low VTE risk profile.

IDH1 has been shown to deactivate tissue factor expression, which is relevant as reactivating tissue factor with demethylating agents can reverse the tumor suppressive phenotype of IDH1 mutant gliomas [35]. Tissue factor/coagulation factor VIIa complex initiates the clotting cascade through cleavage of coagulation factor X, which ultimately results in the formation of a fibrin matrix, and in addition, can modulate intracellular signals through binding to protease-activated receptor 2 [36]. Blocking tissue factor with an inactive coagulation factor VII fragment significantly improved the efficacy of radiation therapy in glioblastoma patients while at the same time inhibiting the procoagulant activity that promotes interactions of glioma and inflammatory cells with the tumor microenvironment [37]. The procoagulant activity of glioma cells became also evident after mixing GBM cells with blood plasma, which resulted in a strong clotting reaction *in vitro* and accelerated xenograft growth after injection into the brain of immune-deficient mice *in vivo* [32]. The role of blood clotting for glioblastoma growth was confirmed by demonstrating delayed intracerebral tumor growth in coagulation factor VIII-deficient hemophilia A mice, which exhibit a severe bleeding phenotype due to the lack of an amplified clotting response downstream of the tissue factor/coagulation factor VIIa complex [38].

The effect of clotting on glioblastoma expansion is greatest in the early phase after tumor cell injection, suggesting similarities to circulating tumor cells where fibrin provides a transitional extracellular matrix until tumor cells are able to organize the microenvironment on their own [39]. The subsequent turnover of the clot matrix by fibrinolysis appears to be an important pro-tumorigenic feature in this context since brain tumor growth *in vivo* was strongly promoted after co-injecting glioblastoma cells with the soluble fraction of clotted plasma that is enriched with monomeric fibrin and fibrin degradation products [32]. These data are backed up by clinical studies that demonstrate significant upregulation of fibrinolysis parameters in glioma patients such as D-Dimers, plasminogen activator inhibitor and tissue-type plasminogen activator side by side with markers of thrombin activation [28,40]. On a functional level, the data indicate that blood clot and its fibrinolysis products represent a critical modification of the tumor microenvironment as they provide adhesive signals for glioma growth and infiltration.

Blood Clotting Promotes Glioma Growth through Glioma Cell Adhesion

The pro-invasive and pro-growth effects of blood clotting can be found in established cell lines as well as in primary tumor cells isolated from patients with glioblastoma, which readily infiltrate 3D matrices of plasma clot *in vitro* [32]. The basement membrane mixture matrigel, on the other hand, appeared less effective in mediating glioma growth and infiltration, suggesting that fibrin and its degradation products make specific contributions to glioma progression. Effective infiltration of GBM cells in clot correlates with overexpression of adhesion receptors of the β1 and β3 integrin family, that support invadopodia formation and GBM proliferation upon binding to specific sites in fibrin and other clot-associated glycoproteins such as fibronectin [32]. This in line with studies on melanoma, renal cell carcinoma and soft tissue sarcoma where integrin αvβ3 plays a key role in lung metastasis by

inducing epithelial mesenchymal transition through adhesive interactions with blood clot [39,41]. In addition, invadopodia formation in fibrin requires the fibrinolytic activity of plasmin, which in turn promotes growth in fibrin-embedded glioblastoma cells. Therefore, these results indicate that invasion and proliferation of glioblastoma cells are supported by overlapping adhesive functions and that activation of the adhesive functions depends on the presence of fibrin fragments.

The overlapping function of invasion and proliferation in clot-embedded GBM cells can be mediated by both integrin β1 and β3, both of which bind and activate focal adhesion kinase (FAK) at tyrosine 397 [32]. This, in turn, leads to recruitment of Src kinase and subsequent activation of critical intracellular signaling pathways such as PI-3K/Akt and p44/42 MAPK [42,43]. FAK has been shown to be upregulated in glioma compared to more benign brain tumors and overexpression of FAK in glioblastoma cells results in increased growth of orthotopic xenografts in immune deficient mice [44,45]. In the context of clotting, activation of FAK has been shown to be critical for fibrin(ogen)- mediated suppression of p53 and p21 in colorectal cancer [46]. Paralleling these data, knocking out FAK in U87MG, U373MG and U343MG glioblastoma cells with CRISPR Cas9 had strong anti-proliferative effects due to upregulation of the cyclin-dependent kinase inhibitors $p21^{CIP1}$ and $p27^{Kip1}$, which resulted in a complete loss of tumorigenicity in immune-deficient mice irrespective of the p53 status [32]. Therefore, these data suggest that glioma cell adhesion to ligands prominently expressed in blood clot could be crucial for cell cycle progression.

The central role of the adhesive machinery in glioma progression was reiterated by mining data from the Cancer Genome Atlas and the Genotype-Tissue Expression projects, which showed stage-dependent upregulation of integrin β1 and β3 in the most aggressive glioma subtypes and down-regulation in less aggressive forms such as IDH1-mutated gliomas [32]. FAK expression did not correlate with glioma progression but the data suggest that FAK phosphorylation may be up-regulated in aggressive and suppressed in less aggressive glioma according to integrin expression. High β1 and β3 integrin expression in glioma correlate with upregulation of pathways involved in epithelial to mesenchymal transition, inflammation, and coagulation, thereby highlighting the functional connection between glioma invasion, microenvironment, and extracellular matrix architecture [32]. This connection is apparent in gliomas of all grades but becomes particularly relevant in low grade gliomas where upregulation of integrin β1 and β3 is associated with significantly reduced patient survival.

Conclusion and Future Directions

The topic of this commentary was the specific contribution of blood clotting to glioma infiltration as described in a recent original research paper by Knowles *et al.* [32]. Taken together, the authors demonstrate that the prothrombotic state of gliomas is associated with the formation and subsequent degradation of fibrin in tumor interstitial spaces. Glioma cell sprouting involves binding of glioma integrins β1 and β3 to clotted plasma and subsequent activation of FAK. Paralleling these data, Knowles *et al.* demonstrate that integrins β1 and β3 are upregulated in patients with aggressive gliomas and that FAK expression is a prerequisite for gliomagenesis in representative murine xenografts [32]. Therefore, the results indicate that adhesive interactions of glioma cells with clot deposits in the tumor extracellular matrix make important contributions to glioma progression.

Anticoagulant therapy in glioma patients is not uncommon due to the high incidence of venous thromboembolism in this patient group and blocking the clot initiating activity of tissue factor with a coagulation factor VII decoy appears to be beneficial in the context of radiation therapy [37]. Treatment of glioma patients with low-molecular heparin due to VTE, on the other hand, does not seem to improve overall survival in a retrospective analysis, but these data are compounded by low overall survival of glioma patients with intracerebral hemorrhage as a complication of anticoagulant therapy [47]. Ultimately, the benefit of anticoagulant therapy in glioma patients with a high risk of developing VTE needs to be prospectively tested in a randomized clinical trial while the role of fibrinolysis for glioma progression should be further explored in preclinical models and early clinical studies.

The standard treatment of glioblastoma consists of maximum safe resection, radiation therapy and maintenance chemotherapy with temozolomide [48]. Additional targeting of αv integrins in glioma tissue and tumor vasculature with the peptidomimetic cilengitide did not improve the survival of glioblastoma patients compared to standard treatment [49]. The reasons that cilengitide did not reach its potential are manyfold, including contradictory functions of αv integrins, intrinsic integrin activation upon binding of the peptidomimetic and also redundancy of the adhesive mechanisms targeted [50,51]. Recognizing that glioma cell adhesion to clotted plasma could be equally mediated by β1 and β3 integrins Knowles *et al.* moved downstream and targeted FAK, which proved to be critical for tumor growth in standard glioblastoma cell lines and xenografts [32]. A series of FAK inhibitors are being tested in clinical trials for the treatment of highly aggressive neoplasms such as pancreatic, lung and ovarian cancer [52]. Considering the wealth of information that can be derived from pathway analysis in glioma tissues, it would appear attractive to further explore the utility of FAK as a treatment target in glioma patients using a bioinformatics approach [53].

Conflicts of Interest

The authors declare no potential conflicts of interest.

References

1. Wen PY, Kesari S. Malignant gliomas in adults. New England Journal of Medicine. 2008 Jul 31;359(5):492–507.
2. Claes A, Idema AJ, Wesseling P. Diffuse glioma growth: a guerilla war. Acta Neuropathologica. 2007 Nov;114(5):443–58.
3. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Cancer Genome Atlas Research Network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010 Jan 19;17(1):98–110.
4. Ruoslahti E. Brain extracellular matrix. Glycobiology. 1996 Jul 1; 6(5):489–92.
5. Mooney KL, Choy W, Sidhu S, Pelargos P, Bui TT, Voth B, et al. The role of CD44 in glioblastoma multiforme. J Clin Neurosci. 2016 Dec;34:1–5.
6. Marino S, Menna G, Di Bonaventura R, Lisi L, Mattogno P, Figà F, et al. The Extracellular Matrix in Glioblastomas: A Glance at Its Structural Modifications in Shaping the Tumoral Microenvironment-A Systematic Review. Cancers (Basel). 2023 Mar 21;15(6):1879.
7. Serres E, Debarbieux F, Stanchi F, Maggiorella L, Grall D, Turchi L, et al. Fibronectin expression in glioblastomas promotes cell cohesion, collective invasion of basement membrane in vitro and orthotopic tumor growth in mice. Oncogene. 2014 Jun 26;33(26):3451–62.
8. Pointer KB, Clark PA, Schroeder AB, Salamat MS, Eliceiri KW, Kuo JS. Association of collagen architecture with glioblastoma patient survival. J Neurosurg. 2017 Jun;126(6):1812–21.
9. Ljubimova JY, Lakhter AJ, Loksh A, Yong WH, Riedinger MS, Miner JH, et al. Overexpression of alpha4 chain-containing laminins in human glial tumors identified by gene microarray analysis. Cancer Res. 2001 Jul 15;61(14):5601–10.
10. Cosset É, Ilmjärv S, Dutoit V, Elliott K, von Schalscha T, Camargo MF, et al. Glut3 Addiction Is a Druggable Vulnerability for a Molecularly Defined Subpopulation of Glioblastoma. Cancer Cell. 2017 Dec 11;32(6):856–868.e5.
11. Janouskova H, Maglott A, Leger DY, Bossert C, Noulet F, Guerin E, et al. Integrin α5β1 plays a critical role in resistance to temozolomide by interfering with the p53 pathway in high-grade glioma. Cancer Res. 2012 Jul 15;72(14):3463–70.
12. Gritsenko PG, Friedl P. Adaptive adhesion systems mediate glioma cell invasion in complex environments. J Cell Sci. 2018 Aug 13;131(15):jcs216382.
13. Haas TL, Sciuto MR, Brunetto L, Valvo C, Signore M, Fiori ME, et al. Integrin α7 Is a Functional Marker and Potential Therapeutic Target in Glioblastoma. Cell Stem Cell. 2017 Jul 6;21(1):35-50.e9.
14. Lathia JD, Gallagher J, Heddleston JM, Wang J, Eyler CE, MacSwords J, et al. Integrin alpha 6 regulates glioblastoma stem cells. Cell stem cell. 2010 May 7;6(5):421–32.
15. Guerrero PA, Tchaicha JH, Chen Z, Morales JE, McCarty N, Wang Q, et al. Glioblastoma stem cells exploit the αvβ8 integrin-TGFβ1 signaling axis to drive tumor initiation and progression. Oncogene. 2017 Nov 23;36(47):6568–80.
16. Zhu Z, Mesci P, Bernatchez JA, Gimple RC, Wang X, Schafer ST, et al. Zika Virus Targets Glioblastoma Stem Cells through a SOX2-Integrin $\alpha_v\beta_5$ Axis. Cell Stem Cell. 2020 Feb 6;26(2):187-204.e10.
17. Vora P, Seyfrid M, Venugopal C, Qazi MA, Salim S, Isserlin R, et al. Bmi1 regulates human glioblastoma stem cells through activation of differential gene networks in CD133+ brain tumor initiating cells. J Neurooncol. 2019 Jul;143(3):417–28.
18. Koh I, Cha J, Park J, Choi J, Kang SG, Kim P. The mode and dynamics of glioblastoma cell invasion into a decellularized tissue-derived extracellular matrix-based three-dimensional tumor model. Sci Rep. 2018 Mar 15;8(1):4608.
19. Huijbers IJ, Iravani M, Popov S, Robertson D, Al-Sarraj S, Jones C, et al. A role for fibrillar collagen deposition and the collagen internalization receptor endo180 in glioma invasion. PLoS One. 2010 Mar 22;5(3):e9808.
20. Herold-Mende C, Mueller MM, Bonsanto MM, Schmitt HP, Kunze S, Steiner HH. Clinical impact and functional aspects of tenascin-C expression during glioma progression. Int J Cancer. 2002 Mar 20;98(3):362–9.
21. Ryu JK, Rafalski VA, Meyer-Franke A, Adams RA, Poda SB, Rios Coronado PE, et al. Fibrin-targeting immunotherapy protects against neuroinflammation and neurodegeneration. Nat Immunol. 2018 Nov;19(11):1212–23.
22. Sakai T, Johnson KJ, Murozono M, Sakai K, Magnuson MA, Wieloch T, et al. Plasma fibronectin supports neuronal survival and reduces brain injury following transient focal cerebral ischemia but is not essential for skin-wound healing and hemostasis. Nat Med. 2001 Mar;7(3):324–30.
23. Landau BJ, Kwaan HC, Verrusio EN, Brem SS. Elevated levels of urokinase-type plasminogen activator and plasminogen activator inhibitor type-1 in malignant human brain tumors. Cancer Res. 1994 Feb 15;54(4):1105–8.
24. Rong Y, Post DE, Pieper RO, Durden DL, Van Meir EG, Brat DJ. PTEN and hypoxia regulate tissue factor expression and plasma coagulation by glioblastoma. Cancer Res. 2005 Feb 15;65(4):1406–13.
25. Brat DJ, Castellano-Sanchez AA, Hunter SB, Pecot M, Cohen C, Hammond EH, et al. Pseudopalisades in glioblastoma are hypoxic, express extracellular matrix proteases, and are formed by an actively migrating cell population. Cancer Res. 2004 Feb 1;64(3):920–7.
26. Brat DJ, Van Meir EG. Glomeruloid microvascular proliferation orchestrated by VPF/VEGF: a new world of angiogenesis research. Am J Pathol. 2001 Mar;158(3):789–96.
27. Li Z, Bao S, Wu Q, Wang H, Eyler C, Sathornsumetee S, et al. Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. Cancer Cell. 2009 Jun 2;15(6):501–13.
28. Sciacca FL, Ciusani E, Silvani A, Corsini E, Frigerio S, Pogliani S, et al. Genetic and plasma markers of venous thromboembolism

in patients with high grade glioma. Clin Cancer Res. 2004 Feb 15;10(4):1312–7.

29. Simanek R, Vormittag R, Hassler M, Roessler K, Schwarz M, Zielinski C, et al. Venous thromboembolism and survival in patients with high-grade glioma. Neuro Oncol. 2007 Apr;9(2):89–95.

30. Daumas-Duport C, Scheithauer B, O'Fallon J, Kelly P. Grading of astrocytomas. A simple and reproducible method. Cancer. 1988 Nov 15;62(10):2152–65.

31. Rodas RA, Fenstermaker RA, McKeever PE, Blaivas M, Dickinson LD, Papadopoulos SM, et al. Correlation of intraluminal thrombosis in brain tumor vessels with postoperative thrombotic complications: a preliminary report. J Neurosurg. 1998 Aug;89(2):200–5.

32. Knowles LM, Wolter C, Linsler S, Müller S, Urbschat S, Ketter R, et al. Clotting Promotes Glioma Growth and Infiltration Through Activation of Focal Adhesion Kinase. Cancer Res Commun. 2024 Dec 1;4(12):3124–36.

33. Unruh D, Schwarze SR, Khoury L, Thomas C, Wu M, Chen L, et al. Mutant IDH1 and thrombosis in gliomas. Acta Neuropathol. 2016 Dec;132(6):917–30.

34. Mir Seyed Nazari P, Riedl J, Preusser M, Posch F, Thaler J, Marosi C, et al. Combination of isocitrate dehydrogenase 1 (IDH1) mutation and podoplanin expression in brain tumors identifies patients at high or low risk of venous thromboembolism. J Thromb Haemost. 2018 Jun;16(6):1121–27.

35. Unruh D, Mirkov S, Wray B, Drumm M, Lamano J, Li YD, et al. Methylation-dependent Tissue Factor Suppression Contributes to the Reduced Malignancy of IDH1-mutant Gliomas. Clin Cancer Res. 2019 Jan 15;25(2):747–59.

36. Mackman N, Tawil N, Rak J. Tissue factor at the crossroads of coagulation and radiation response in glioblastoma. J Thromb Haemost. 2024 Jan;22(1):3–6.

37. Jeon HM, Kim JY, Cho HJ, Lee WJ, Nguyen D, Kim SS, et al. Tissue factor is a critical regulator of radiation therapy-induced glioblastoma remodeling. Cancer Cell. 2023 Aug 14;41(8):1480–97.e9.

38. Bi L, Lawler AM, Antonarakis SE, High KA, Gearhart JD, Kazazian HH Jr. Targeted disruption of the mouse factor VIII gene produces a model of haemophilia A. Nat Genet. 1995 May;10(1):119–21.

39. Knowles LM, Gurski LA, Engel C, Gnarra JR, Maranchie JK, Pilch J. Integrin αvβ3 and fibronectin upregulate Slug in cancer cells to promote clot invasion and metastasis. Cancer Res. 2013 Oct 15;73(20):6175–84.

40. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol. 2009 Sep 1;27(25):4124–9.

41. Malik G, Knowles LM, Dhir R, Xu S, Yang S, Ruoslahti E, et al. Plasma fibronectin promotes lung metastasis by contributions to fibrin clots and tumor cell invasion. Cancer Res. 2010 Jun 1;70(11):4327–34.

42. Sonoda Y, Watanabe S, Matsumoto Y, Aizu-Yokota E, Kasahara T. FAK is the upstream signal protein of the phosphatidylinositol 3-kinase-Akt survival pathway in hydrogen peroxide-induced apoptosis of a human glioblastoma cell line. J Biol Chem. 1999 Apr 9;274(15):10566–70.

43. Ding Q, Grammer JR, Nelson MA, Guan JL, Stewart JE Jr, Gladson CL. p27Kip1 and cyclin D1 are necessary for focal adhesion kinase regulation of cell cycle progression in glioblastoma cells propagated in vitro and in vivo in the scid mouse brain. J Biol Chem. 2005 Feb 25;280(8):6802–15.

44. Jones G, Machado J Jr, Tolnay M, Merlo A. PTEN-independent induction of caspase-mediated cell death and reduced invasion by the focal adhesion targeting domain (FAT) in human astrocytic brain tumors which highly express focal adhesion kinase (FAK). Cancer Res. 2001 Aug 1;61(15):5688–91.

45. Wang D, Grammer JR, Cobbs CS, Stewart JE Jr, Liu Z, Rhoden R, et al. p125 focal adhesion kinase promotes malignant astrocytoma cell proliferation in vivo. J Cell Sci. 2000 Dec; 113 Pt 23:4221–30.

46. Sharma BK, Mureb D, Murab S, Rosenfeldt L, Francisco B, Cantrell R, et al. Fibrinogen activates focal adhesion kinase (FAK) promoting colorectal adenocarcinoma growth. J Thromb Haemost. 2021 Oct;19(10):2480–94.

47. Mantia C, Uhlmann EJ, Puligandla M, Weber GM, Neuberg D, Zwicker JI. Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin. Blood. 2017 Jun 22;129(25):3379–85.

48. Stupp R, Mason WP, Van Den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. New England journal of medicine. 2005 Mar 10;352(10):987–96.

49. Stupp R, Hegi ME, Gorlia T, Erridge SC, Perry J, Hong YK, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2014 Sep;15(10):1100–8.

50. Alghisi GC, Ponsonnet L, Rüegg C. The integrin antagonist cilengitide activates αVβ3, disrupts VE-cadherin localization at cell junctions and enhances permeability in endothelial cells. PloS one. 2009 Feb 12;4(2):e4449.

51. Reynolds LE, Wyder L, Lively JC, Taverna D, Robinson SD, Huang X, et al. Enhanced pathological angiogenesis in mice lacking β3 integrin or β3 and β5 integrins. Nature medicine. 2002 Jan 1;8(1):27–34.

52. Schlaepfer DD, Ojalill M, Stupack DG. Focal adhesion kinase signaling–tumor vulnerabilities and clinical opportunities. Journal of Cell Science. 2024 Jul 15;137(14):jcs261723.

53. Liu X, Yi J, Li T, Wen J, Huang K, Liu J, et al. DRMref: comprehensive reference map of drug resistance mechanisms in human cancer. Nucleic acids research. 2024 Jan 5;52(D1):D1253–64.