Caveolin-1, caveolae, and glioblastoma

Marie-Odile Parat and Gregory J. Riggins

University of Queensland School of Pharmacy, PACE, Woolloongabba, QLD, Australia (M-O.P.); Ludwig Collaborative Laboratory, Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland (G.J.R.)

Glioblastoma multiforme (GBM) is the most common malignant brain tumor and is characterized by high invasiveness, poor prognosis, and limited therapeutic options. Biochemical and morphological experiments have shown the presence of caveolae in glioblastoma cells. Caveolae are flask-shaped plasma membrane subdomains that play trafficking, mechanosensing, and signaling roles. Caveolin-1 is a membrane protein that participates in the formation of caveolae and binds a multitude of signaling proteins, compartmentalizing them in caveolae and often directly regulating their activity via binding to its scaffolding domain. Caveolin-1 has been proposed to behave either as a tumor suppressor or as an ongogene depending on the tumor type and progress. This review discusses the existing information on the expression and function of caveolin-1 and caveolae in GBM and the role of this organelle and its defining protein on cellular signaling, growth, and invasiveness of GBM. We further analyze the available data suggesting caveolin-1 could be a target in GBM therapy.

Keywords: caveolae, caveolin-1, EGF receptor, glioblastoma, uPA.

Caveolin-1 and Caveolae

Caveolae are plasma membrane subdomains of distinct lipid and protein compositions present in many mammalian cells. These flask-shaped organelles play multiple roles in cell physiology, including serving as signaling platforms for numerous pathways, as clathrin-independent routes of endocytosis, and as mechanical stress sensors.1 The functions of caveolae require proteins of the caveolin family and, most importantly, caveolin-1, a membrane integral protein key to caveola structure. Caveolins oligomerize and, in concert with cytoplasmic proteins of the cavin family, allow caveola to form.2,3 Caveolin-1 exhibits an unusual conformation with a short membrane-inserted domain and its N- and C-termini both facing the cytosol. Caveolin-1 C-terminus is triply palmitoylated,4 and the N-terminus encompasses a putative cholesterol-binding domain,5 a scaffolding domain,6 and functionally important serine7 and tyrosine8 phosphorylation sites.

In addition to participating in caveola formation, caveolin-1 is known to directly interact via its scaffolding domain with multiple signaling proteins and to regulate their activity. These proteins include important regulators of cell transformation and growth.9 Furthermore, caveolin-1 is best known as a membrane protein, but noncaveolar, soluble, and secreted forms of caveolin-1 have also been described and seem to have biological functions (reviewed in Parat1). Both caveolar and noncaveolar caveolin-1 are involved in modulating cancer cell growth and metastasis. This is reviewed elsewhere9–12 and will only be briefly mentioned to keep our review focused on glioblastoma multiforme (GBM).

Caveolin-1 has been proposed to behave as a tumor suppressor or an ongogene, depending on the tumor type. Initially, caveolin-1 was regarded as a tumor suppressor. Its expression increased with differentiation, and its loss was associated with de-repression of growth-promoting signaling. The gene encoding caveolin-1 was mapped to the human chromosome 7q31.1, where a known fragile site frequently deleted in human cancers is also located.13 Mutation or loss of caveolin-1 expression because of heterozygosity or promoter hypermethylation were described in multiple cancers, such as breast, ovarian, small cell lung, small cell bladder, or colorectal carcinomas (reviewed in van Golen9). In contrast, overexpression of caveolin-1 was reported in a number of malignancies, including prostate cancer. In prostate cancer, caveolin-1 expression and secretion are increased and caveolin-1 contributes to tumor angiogenesis, growth, and metastasis.14–16 In addition to being tumor type-specific, caveolin-1 expression is now accepted to be tumor stage-specific, with decreased expression favoring proliferation and survival at early stages, followed by upregulated expression.
accompanied by invasiveness, metastasis, and multidrug resistance at later stages. A distinct role for caveolin-1 in tumor cells versus caveolin-1 expressed by stromal cells is emerging, bringing increasing complexity to the picture. Lastly, recent evidence suggests that there might be a different role and a different significance for caveolin-1 in cancer cells, depending on its subcellular localization, with noncaveolar caveolin-1 increasing tumor aggressiveness.19,20

In addition to caveolins, caveola formation and functions are now known to involve a family of cytoplasmic proteins named cavins. Cavin-1, or polymerase I and transcript release factor (PTRF), is the only cavin indispensable for caveola formation.21 It also plays roles in transcription termination via interaction with RNA polymerase I22,23 and in regulation of type I collagen gene expression by interacting with a DNA-binding transcription factor.24 Of the other members of the cavin family, the serum-deprivation response (SDPR/cavin-2) participates in caveolar membrane curvature,25 the SDR-related gene product that binds to C kinase (SRBC/cavin-3) regulates caveolae budding,26 and the muscle restricted coiled-coil protein (MURC/cavin-4) is muscle specific.21 Dysregulated expression of proteins from the cavin family in cancer is documented.27,28 The expression of PTRF usually mirrors that of caveolin-1 in normal and tumor tissue.21,27 When not expressed, however, the absence of PTRF results in the expression of noncaveolar caveolin-1,2 which may have functional consequences.19,29 PTRF was identified as a gene increasing chemoresistance of colorectal cancer cells.30 However, caveolin-1 expression has been documented in neurons and glia. The abundance of caveolin-1 mRNA varies in different parts of the brain.46

Expression and Functions of Caveolin-1 in Astrocytes

Much less is known about caveolin-1 expression and functions in the different cell types of the brain, compared with other cell types, in part because the brain expresses much less caveolin-1 than do other tissues. However, caveolin-1 expression has been documented in neurons and glia. The abundance of caveolin-1 mRNA varies in different parts of the brain.46

Caveolae have been observed in early studies of optic nerve astrocytes using thin section and freeze fracture electron microscopy and were abundant in areas of the plasma membrane facing other astrocytes (up to 17 caveolae per micrometer2) or opposed to myelin sheaths.47 Caveolae were also found in host astrocytes invading neural transplants48 or in cultured rat primary astrocytes.49 In a comprehensive study of caveolin-1 expression in astrocytes, caveolin-1 alpha (full length) isoform was detected by Western blot analysis in low-density, detergent-insoluble microdomains from type 1 astrocytes.50 Immunofluorescence microscopy of primary cells revealed a punctate pattern resembling that of other caveolin-1-expressing cells. Caveolin-1 messenger RNA was detected in primary astrocytes, both by Northern analysis and reverse-transcriptase polymerase chain reaction.50 Caveolin-2, which is co-expressed and co-oligomerizes with caveolin-1 in most tissues, is also present in astrocytes.51

The functions of caveolin-1 and caveolea in astrocytes are consistent with what is known in other cell types: they participate in signaling and trafficking. Studies specifically identifying caveolar signaling in astrocytes include biochemical evidence that endothelin-1 mitogenic signaling leading to FAK and ERK activation is localized in caveolea.62 In addition, reactive oxygen species-induced activation of ERK in astrocytes was shown to require caveolin-1 expression.63
Calcium signaling molecules, such as TRPC1, IP3R2, and ryanodine receptor, were co-fractionated with caveolin-1 in astrocytes detergent insoluble fractions. Another example is interleukin beta receptor type 1 (IL-1RI)/Toll-like receptor type 4 (TLR4), shown to be recruited to caveolae after activation and to initiate downstream signaling in caveolae. Of interest, this pathway can be activated by ethanol and may mediate ethanol-induced inflammatory damage in the brain. In astrocytes, caveolin-1 was also documented to compartmentalize and interact with multidrug resistance protein -1 (MDR1), also named P-glycoprotein-1 (P-gp), which participates in the blood-brain barrier (BBB) function.

Caveolae have also been proven to play trafficking functions in primary cultured astrocytes. Albumin endocytosis was localized to caveolae by electron microscopy and required the expression of caveolin-1. Caveolae also internalize the CCR2 receptor-bound ligand MCP-1, and caveolin-1 siRNA reduced calcium influx and astrocyte chemotaxis to MCP-1. Caveolin-1 further regulates cell surface expression and endocytosis of the excitatory amino acid carrier 1 (EAAC1) glutamate transporter in neuron/astrocytes mixed cultures. Caveolin-1 is known to participate in cholesterol trafficking. Accordingly, in astrocytes, caveolin-1 was shown to participate in cholesterol eflux to generate HDL, and to mediate the retrograde cholesterol transport from the plasma membrane to the Golgi in response to amyloid beta protein.

Little is known about the regulation of caveolin-1 expression in astrocytes. A study determined that a single dose of gamma ray irradiation increased caveolin-1 expression in spinal cord astrocytes 1 day after irradiation. In another study, primary astrocytes isolated from the striatum underwent caveolin-1 down-regulation at the protein and mRNA levels in response to cAMP and TGF-α. TGF-α–induced downregulation of caveolin-1 expression was MAP kinase-independent but PI3-kinase dependent. Furthermore, this regulation was restricted to the striatum because it was not observed in astrocytes from other brain regions. The authors hypothesized that downregulation of caveolin-1 was part of a feedback regulatory loop involving PI3K, promoting the expression of the glutamate transporter GLT-1 during astrocyte differentiation.

Caveolin-1 and Caveolae in GBM Cells

The literature widely describes an increased expression of caveolin-1 in GBM (Table 1). However, some nuances must be kept in mind when looking at these results. First, GBMs are a mix of tumor and infiltrating nontumor cells. GBM lysates are likely to contain abundant caveolin-1–expressing cells (microglia, macrophages, and endothelial cells, in addition to GBM cells), compared with neurons in normal brain tissue, known to express very little caveolin-1. Moreover, there seems to be heterogeneity in caveolin-1 expression between tumor cells in each GBM, indicating that caveolin-1–positive and negative tumor cells coexist in GBM.

Identification of differentially expressed genes in human GBM comparing RNA pooled from 2 GBMs to RNA pooled from normal human brain identified a 5.2-fold overexpression of caveolin-1 mRNA in GBM. Similarly, caveolin-1 mRNA was found to be increased in the GBM cell line U87MG, compared with primary human astrocytes, and in tumors, compared with nonmalignant brain tissue. In contrast, caveolin-2 and -3 mRNA were reported to be decreased in a GBM cell line, compared with primary astrocytes.

In another study, caveolin-1 immunoreactivity was detected in astrocytic-derived tumors, with very intense staining in GBMs, whereas no immunoreactivity was detected in normal brain glia or neurons. Both staining pattern (membrane vs intracellular) and intensity were associated with tumor grade. Immunofluorescence analysis and flow cytometry confirmed with glioma cell lines and primary cultures the results observed in tissue sections.

In various human GBM-derived cell lines (T98G, U87MG, U118MG, U138MG, and U373MG) and in rat primary astrocytes and transformed astroglial cell lines (C6 and DITNC1) abundant caveolin-1 mRNA and protein levels were detected, although with variable levels. Nucleotide sequence analysis further indicated that no mutations were present in any of the cell types. Of importance, caveolin-1 low-buoyant density and caveola formation were shown to be maintained. Caveolae were still apparent when the cells were grown ectopically in mice. Accordingly, caveolin-1 have also been reported after electron microscopy observation of GBM specimens. Caveolae endocytosis has been proposed as a route of entry into GBM cells (T98G) for uptake of therapeutic siRNA dendriplexes, further indicating that caveolae in GBM cells are functional, and that they may be taken advantage of for therapeutic delivery.

The published information about caveolin-1 increased expression in GBM is recapitulated in Table 1. We found no literature on quantification of caveolin-1 tyrosine 14 phosphorylation in GBM or on the expression of the caveolae-forming protein, PTRF/ cavin-1, in GBM.

Antitumor Therapies of Glioma Are Associated With/Act Via Upregulation of Caveolin-1

An increased expression of caveolin-1 has been shown to be associated with and/or mediate the action of some anti-glioma therapies. One such therapeutic class are the inhibitors of the catalytic light chain (xCT) of system xc-, a Na+–independent heterodimeric aminoacid transport system that allows cystine uptake in exchange for glutamate release. Glioma cells produce high concentrations of glutamate using this transporter, which causes toxicity to healthy neurons surrounding the...
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Abbreviation: GBM, glioblastomas.
tumor. Furthermore, because glioma cells rely on this transporter for cystine uptake, inhibition of system x-c increases intracellular glutathione depletion resulting in apoptosis.\(^7^3\) In tumor cells, xCT inhibition was shown to cause reactive oxygen species–mediated caveolin-1 upregulation and inhibition of tumor cell invasion.\(^7^4\) Another example is the alkylation agent temozolomide, indicated in GBM treatment. Temozolomide also increased caveolin-1 expression in experimental GBM grown in vivo.\(^7^5\) Of interest, the authors showed that caveolin-1 exogenously applied to GBM cells decreased invasion.\(^7^5\) Caveolin-1 expression was also increased in glioma cells exposed to ionizing radiation;\(^7^6\) however, in this study, caveolin-1 was proposed to be upregulated in a transcriptionally independent fashion in multiple cell types in response to genotoxic stress and to participate in DNA damage repair.

One group of investigators has endeavored to directly manipulate caveolin-1 expression levels in the cell line U87MG and tested the resulting phenotype of the cells and their changes in gene expression. They showed that forced expression of caveolin-1 decreased proliferation, clonogenicity, and invasion, whereas downregulation of caveolin-1 had the opposite effect.\(^7^7\) Gene expression analysis in this study indicated that caveolin-1 controlled genes involved in the regulation of cell invasion and metastasis, for example, the serine protease inhibitor PAI-1 (inversely proportional to caveolin-1) and genes involved in the regulation of cell adhesion, such as integrins (also inversely proportional to caveolin-1 expression).\(^7^7\) The study further focused on integrin α5β1 and showed that GBM cells with caveolin-1 siRNA (and, thus, increased α5) were more sensitive to the α5β1 integrin antagonist SJ749. Furthermore, a feedback regulation was suggested, because overexpression of the α5 subunit in turn upregulated caveolin-1 expression.\(^7^7\)

**EGFR and Caveolin-1 in GBM**

The EGFR is proposed to bind to caveolin-1 via its caveolin-1 binding motif located in the kinase domain\(^3^3\) and to be maintained in an inactive state by the interaction, moving out of caveolae upon EGF stimulation.\(^7^8\) The migration or EGFR out of caveolae requires the autophosphorylation of at least one tyrosine residue in the receptor regulatory domain and the binding of EGF.\(^7^8\) Several major mutated variants of EGFR have been identified in GBM, the most common being variant III (EGFRvIII), caused by an 801 bp in frame deletion of exons 2~7, leading to the expression of a constitutively autophosphorylated receptor lacking a portion of the EGF binding domain that contributes to an aggressive phenotype in GBM.\(^7^9\) In GBM cells, wild-type EGFR was confirmed to colocalize with lipid rafts and caveolin-1 and to associate with caveolae in a phosphorylation-dependent fashion, because EGF-induced phosphorylation of the receptor resulted in EGFR dissociation from caveolae.\(^6^9\) In contrast, constitutively active EGFRvIII was predominantly cytoplasmic and did not associate with the caveolin-1 scaffolding domain unless cells were exposed to a tyrosine kinase inhibitor to prevent receptor phosphorylation.\(^6^9\) Furthermore, disrupting rafts induced ligand-independent tyrosine phosphorylation of EGFR.\(^6^9\) Phosphorylation-dependent sequestration of EGFR in caveolae was thus proposed to have the potential to shut down constitutive or EGF-induced signaling in GBM.\(^6^5\) Of interest, low caveolin-1 expression was shown to correlate with EGFR overexpression in anaplastic astrocytomas.\(^6^7\) In contrast, caveola disruption using methyl-β cyclohextrin was shown to disrupt GBM chemotaxis to EGF,\(^8^0\) and simvastatin prevented astrocyte activation after traumatic brain injury by decreasing caveolin-1 expression and reducing EGFR phosphorylation.\(^8^1\)

**Matrix Proteases and Caveolae in GBM**

Proteolysis is an essential component of the invasion process through the disruption of basement membrane, extracellular matrix, and cell-cell junctions. Two major proteolytic systems, namely the urokinase and the matrix metalloproteinase (MMP) systems, have been documented to promote GBM invasion. Furthermore, enzymes from both systems have been shown to synergistically interact in GBM.\(^8^2,8^3\)

The receptor for urokinase-type plasminogen activator (uPAR) both participates in the activation of uPA, which promotes invasion and angiogenesis via plasminogen activation and further controls intracellular signaling, integrin activation, and fibronectin polymerization. uPAR was reported to be overexpressed in GBM.\(^8^4\) Caveolin-1 is considered to be an adaptor protein regulating integrin function\(^8^5,8^6\) that mediates uPAR-dependent activation of Src and EGFR.\(^8^7,8^8\) Both caveolin-1 and the GPI-anchored urokinase receptor uPAR interact with β1 integrins in a complex that regulates adhesion and signaling through Src-family kinases and focal adhesion kinase (FAK). The formation of such functional units contributes to migration and invasion.\(^8^9\) In GBM, uPAR controls invasion via proteolysis and key intracellular signaling pathways, including PI3k/Akt and Notch signaling.\(^9^0,9^1\) Not surprisingly, uPA and/or uPAR are well-known therapeutic targets in GBM. In addition, the crosstalk between uPAR signaling and EGFR signaling suggests that uPAR and EGFR are valid combined targets for GBM therapy.\(^9^2\) The role of caveolin-1 in major signaling pathways relevant to GBM is depicted in Fig. 1.

Matrix metalloproteases are a family of endopeptidases mediating pericellular proteolysis in tumor cell invasion through digestion of the extracellular matrix (ECM), release of ECM growth factors, and interaction with adhesion molecules, thereby controlling the tumor microenvironment.\(^6^5\) MMPs exist as secreted latent soluble forms activated by proteolysis, for example, the gelatinases MMP-2 and MMP-9, and as membrane-inserted enzymes, for example, membrane type
MT1-MMP. MT1-MMP degrades ECM molecules, including constituents of the brain and glioma ECM, and further activates pro-MMP2 into MMP2. Both quantitative expression of MT1-MMP and its subcellular localization have been documented to play a key role in GBM cell migration and invasion. MT1-MMP is localized in caveolae and interacts with caveolin-1. Caveolin-1 also directly inhibits MEK-1 and ERK-2 downstream of the EGFR activation. UPA forms a complex with integrins and caveolin-1 that signals through Src family kinases and focal adhesion kinase (FAK). Via interacting with the uPA receptor and MT1-MMP, caveolin-1 spatially controls extracellular proteolysis, including growth factor release from the extracellular matrix, and basement membrane degradation.

Caveolin-1 Negatively Regulates P-gp: Potential Role in Preventing Multidrug Resistance

The permeability glycoprotein (P-gp) transporter is an efflux pump that participates in multidrug resistance by promoting efflux of xenobiotics and, thus, decreasing drug accumulation in the cells. It is highly expressed by endothelial cells and astrocytes at the BBB, including the BBB of brain tumors, where it interacts with the caveolin-1 scaffolding domain. The interaction with caveolin-1 negatively regulates P-gp transport activity, thereby promoting intracellular transport of drugs. In this context, increasing caveolin-1-mediated inhibition of P-gp in GBM cells might increase sensitivity to chemotherapeutic agents.

Conclusion and Perspectives

There is increasing evidence that caveolin-1 and caveolae play multiple signaling and trafficking functions in GBM marking this organelle and/or its defining protein as targets for a disease that desperately needs novel therapeutic options. Caveolae have been scrutinized as drug delivery routes, and because GBM’s caveolae might be used to promote endocytosis of material with potential therapeutic value to cells (eg, pharmacological agents and genetic material). Demonstrated uptake of therapeutic siRNA dendriplexes in GBM cells provides
promising proof of concept for this strategy. In addition, the caveolin-1 inhibitory effect on P-gp has the potential to increase drug delivery to GBM cells via action on the transporter at the BBB and GBM cell levels.

Both increasing and decreasing caveolin-1 expression have been proposed as cancer therapeutic approaches,\(^9\) using ectopic expression of caveolin-1 or siRNA, respectively. In GBM, caveolin-1 overexpression rather than downregulation induced a reduction in proliferation, clonogenicity, and migration.\(^{77}\) This may seem counterintuitive, as caveolin-1 is reported to be overexpressed in GBM compared with normal astrocytes. However, caveolin-1 exerts multiple effects (direct inhibition, receptor endocytosis from cell surface, and compartmentalization) on multiple signaling pathways key to GBM growth and invasion. Another means of taking advantage of caveolin-1 tonic inhibition on signaling molecules that has proven to be effective in vivo is to mimic the inhibitory effect by using the caveolin-1 scaffolding domain peptide, fused to an internalization sequence allowing cellular uptake.\(^{101}\)

Although initially designed to control nitric oxide production in endothelial cells, this peptide, named cavertratin, was shown to suppress nerve growth factor–induced MAPK activation in oligodendrocytes, indicating that inhibition of growth factor receptors can be achieved in macroglial cells.\(^{102}\) Mutations of specific amino acids in the scaffolding domain peptide can perturb, rather than reproduce, the interaction with target signaling molecules,\(^{103}\) and although this has been worked out for the interaction of caveolin-1 with eNOS, the concept could be applied to generate peptides affecting growth factor receptor inhibition. Lastly, an indirect method to modulate caveolin-1 expression and caveolae function is to interfere with cholesterol homeostasis with use of statins. Of interest, simvastatin decreased caveolin-1 expression and reduced EGFR phosphorylation in astrocytes.\(^{81}\) It is likely that caveolin-1 will be evaluated as a target in GBM in the near future, alone or in combination with currently available therapies to increase their efficacy.

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