

The Role of Caveolar Proteins in Glioblastoma

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Abstract – Glioblastoma multiforme (GBM) is the most well-known threatening cerebrum cancer and is portrayed by high intrusiveness, helpless guess, and restricted restorative choices. Biochemical and morphological trials have shown the presence of caveolae in glioblastoma cells. Caveolae are cup molded plasma layer subdomains that play dealing, mechanosensing, and flagging jobs. Caveolin-1 is a layer protein that takes an interest in the development of caveolae and ties a huge number of flagging proteins, compartmentalizing them in caveolae and frequently straightforwardly managing their movement by means of restricting to its framework area. Caveolin-1 has been proposed to act either as a cancer silencer or as an oncoprotein relying upon the growth type and progress. This audit examines the current data on the articulation and capacity of caveolin-1 and caveolae in GBM and the job of this organelle and its characterizing protein on cell flagging, development, and obtrusiveness of GBM. We further investigate the accessible information proposing caveolin-1 could be an objective in GBM treatment.

Keywords – Caveolae, Caveolin-1, EGF Receptor, Glioblastoma, uPA

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INTRODUCTION

Strong growths are presented to osmotic and mechanical anxieties. Both preclinical and clinical examinations show that growths are by and large inadequately perfused, and cancer interstitial liquid tension (IFP) is expanded contrasted with ordinary tissue, with both expanded hydrostatic strain and oncotic pressure. This outcomes from a mix of elements, including wasteful lymphatic seepage of dissolvable proteins, flawed and broken veins, expanded fibroblast numbers, thicker collagen strands and aggregation of provocative element emitting cells. Furthermore, on account of strong cancers developing inside the cerebrum, the space restriction that the skull makes brings about additional pressure as the growth develops; patients with mind cancers experience expanded intracranial pressure.

Caveolae are carafe molded plasma layer subdomains that need, for gathering, support and capacities, proteins from two families, the film implanted caveolins and the cytoplasmic cavins. Caveolae serve significant jobs in flagging, film homeostasis and mechanosensing. Caveolae additionally add to surface region homeostasis, as they level reversibly to permit immediate layer strain buffering.⁶ The tension detecting abilities of caveolae and the mechanotransduction limits of caveola-shaping proteins have pathophysiological results on cardiovascular or muscle function. In glioblastoma (GBM), caveolae or caveola-framing proteins have

been proposed to be significant in the guideline of EGFR flagging, protection from treatment and exosome-intervened cell-cell communication.⁹⁻¹¹ Moreover, the outflow of both caveolin-1 and CAVIN1 are expanded in GBM contrasted with ordinary examples and are related with more limited patient endurance time and corresponded with articulation of the framework proteases uPA and gelatinases.

Lattice proteases are key middle people of the obtrusiveness of GBM, which thus adds to the illness especially helpless forecast. A few flagging pathways known to be enacted in GBM bring about expanded protease articulation. On the other hand, framework proteases, for example, gelatinases or uPA act through both corruption of the mind extracellular network and the enactment of favorable to transitory signalling.¹³ We have recently exhibited that openness of GBM follower cell lines or oncospheres to osmotic and hydrostatic or radial strain actuates an expansion in GBM intrusive potential in vitro. In the current review, we examined whether caveolae intervene the favorable to intrusive reaction to strain in GBM cells.

Glioblastoma (GBM) is the most widely recognized essential cerebrum malignant growth. The normal endurance time for most of patients is around 15 months after analysis. A significant component of GBM that adds to its helpless guess is its high intrusiveness. Caveolae are plasma film

subdomains that take an interest in various organic capacities. Caveolin-1 and Caveolae Associated Protein 1 (CAVIN1), previously named Polymerase I and Transcript Release Factor, are both vital for caveola arrangement. We estimated that high articulation of caveola-shaping proteins in GBM advances intrusiveness by means of adjustment of the creation of grid debasing compounds.

OBJECTIVE OF STUDY

1. Study on the role of caveolar proteins in Glioblastoma.
2. Study on glioblastoma.

RESEARCH METHODOLOGY

Materials

RPMI-1640 medium, Opti-MEM™ medium, geneticin, lipofectamine 3000, trypsin-EDTA, penicillin/streptomycin, Coomassie splendid blue R-250 Pierce™ BCA Protein Assay Kit and continuous PCR reagents were bought from Life Technologies. The 40% acrylamide/bis arrangement was from Bio-Rad. CultreCoat® 24-well plates with BME-Coated Inserts were from Bio Scientific Pty. Ltd. CultreCoat® 96 Well Medium BME Cell Invasion Assay Kit was from Bio Scientific Pty. Ltd. The caveolin-1 essential neutralizer was from Cell Signaling Technology, and CAVIN1 essential immune response was from Proteintech®. ECLTM Anti-Rabbit IgG was bought from GE Healthcare Science. Different reagents were bought from Sigma-Aldrich except if in any case indicated.

Cell culture

Human GBM cell line U118 was refined in RPMI medium enhanced with 10% (v/v) FBS, 100 U/mL penicillin and 100 µg/mL streptomycin. U251 cells were transfected with plasmids encoding shRNA to CAV1 or control shRNA utilizing Transpass™ as per the maker's guidelines. Steadily transfected clones were secluded after determination utilizing 250 µg/mL G418 and tried utilizing Western blotch investigation with against CAV1 and hostile to CAVIN1 essential antibodies. All cell lines were brooded at 37°C with 5% CO₂.

Generation of CAVIN1 or caveolin-1

CRISPR knockout U251 cell lines CAV1 or CAVIN1 bunched routinely interspaced short palindromic reshapes (CRISPR) knockout U251 cell lines were created at the Queensland Facility for Advanced Genome Editing (QFAGE), Institute for Molecular Bioscience, The University of Queensland. For every quality, three aide RNA (gRNA) focusing on the coding succession of exon1 or exon2 was planned utilizing the free internet based apparatus <http://crispr.mit.edu/>. For CAVIN1, the arrangements

were gRNA1: ATCAAGTCGGACCAGGTGAA, gRNA2: GCTCACCGTATTGCTCGTGG, gRNA3: GTCAACGTGAAGACCGTG CG; for caveolin-1, the successions were gRNA1: ATGTTGCC CTGTTCCCGGAT, gRNA2: AGTGTACGACGCGCACACCA, gRNA3: GTTTAGGGTTCGCGGTTGACC. Ribonucleoprotein (RNP) buildings were shaped by blending 20 pmol of each orchestrated gRNA (crRNA + tracrRNA, IDT) with 20 pmol of spCas9 protein. Gathered RNPs were joined with 200 000 U251 cells and transfected utilizing a Lonza Nucleofector 4D gadget (pack SE, program DS-138). Fortyeight hours post-transfection, genomic DNA of mass transfected cell pools was removed and the altering viability was affirmed by T7E1 (T7 Endonuclease I) measure and Sanger sequencing investigation. Pooled cells transfected with the three gRNA were tried for deficiency of CAV1 and CAVIN1 protein articulation.

siRNA-interceded CAV1 or CAVIN1 knockdown 2.4 CAV1 or CAVIN1 articulation was restrained in U251 cells utilizing Stealth siRNAs. The CAV1 Stealth siRNAs (HSS141466, HSS141467 and HSS141468), CAVIN1 Stealth siRNAs (HSS138488, HSS138489 and HSS178652) and Stealth RNAi™ siRNA Negative Control, Med GC were bought from Life Technologies (Life Technologies). The transfection was directed utilizing Lipofectamine 3000 as past depicted. After the transfection, the cells were parted as needed for tests.

Osmotic stress

The different osmolality media were ready as recently portrayed 12 and controlled utilizing an OSMOMAT 3000 fundamental edge of freezing over osmometer (Gallay) adjusted utilizing 300 and 500 mOsmol/kg principles. The osmolalities utilized to concentrate on cell reactions were chosen in light of cell endurance at 48 hours For U118, U87, U251 and shRNA U251 cells, the most noteworthy non-harmful osmolality was 440 mOsmol/kg. For CRISPR-Cas9 cells, the most noteworthy hyperosmolality was 360 mOsmol/kg. 1.0 × 10⁶ cells were cultivated in 12-well plates and brooded at 37°C with 5% CO₂ for 24 hours After 24 hours, cells were flushed with sans serum medium two times and 1 mL of without serum mechanism of fluctuating osmolality was added to each well and hatched for 48 hours The medium was gathered and centrifuged at 935 g for 5 minutes then, at that point, put away at -80°C until examination.

Hydrostatic pressure treatment

5.0 × 10⁶ cells were cultivated in T25 cup and brooded at 37°C with 5% CO₂ for 24 hours Cells were flushed with without serum medium two times and added with 3 mL of without serum medium containing 25 µmol/L HEPES. The flagon cover was fitted with a three-way stopcock (BD

Connecta™), and strain expanded to 30 mm Hg utilizing a sphygmomanometer. The strain was kept up with by shutting the stopcock, and the cells were brooded for 48 hours. A cup with an air-penetrable top was utilized as control. The medium was gathered and centrifuged at 935 g for 5 minutes then, at that point, put away at -80°C until examination.

MTT assay

The cell suitability was tried utilizing the 3-[4,5-dimethylthiazole2-yl]-2,5-diphenyltetrazolium bromide (MTT) examine as past portrayed. The UV absorbance was perused with an iMark™ microplate absorbance peruser at 595 nm (Bio-Rad Laboratories). Foundation absorbance was deducted, and results were communicated as the rate reasonability of control cells.

In gel zymography

Gelatinases and uPA in media adapted by various cell lines were estimated by gelatin or casein-plasminogen zymography as past depicted. The gels were examined, and uPA, MMP-2 and MMP-9 were measured by densitometry utilizing Image J (v1.48) programming.

Quantitative RT-PCR

The mRNA articulation of explicit qualities and epithelial-to-mesenchymal progress (EMT) markers levels was estimated by ongoing converse transcriptase-polymerase chain response (constant RTPCR). Complete RNA was segregated and purged utilizing the PureLink® RNA Mini Kit (Life Technologies). The complete RNA (2000 ng) was opposite interpreted utilizing the High-Capacity cDNA Reverse Transcription Kit (Life Technologies). Quantitative ongoing PCR was performed utilizing TaqMan™ Fast Universal PCR Master Mix (Life Technologies) in a StepOnePlus 7500 constant PCR framework (Applied Biosystems). The groundworks of target qualities utilized for this examination were TaqMan™ Gene Expression Assay for human PLAU (Hs01547054_m1), PLAU (Hs00958880_m1), MMP-2 (Hs01548727_m1), MMP-9 (Hs00957562_m1), CAV1 Twist (Hs00971716_m1), CAVIN1 (Hs00396859_m1), AQP1 (Hs01028916_m1), Snail-1 (Hs00195591_m1), Snail-2 (Hs00161904_m1), (Hs01675818_s1), Vimentin (Hs00185584_m1) and N-cadherin (Hs00983056_m1). Relative measurement was finished by reference to 18S ribosomal RNA (18S rRNA) and analysed using the comparative critical threshold (Ct) method.

Electron microscopy

U251 cells were handled for transmission electron microscopy in 3 cm dishes utilizing standard protocols. Images were taken at an amplification of 12 000x. The quantity of surface clathrin-covered pits (CCP), surface caveolae (where a reasonable

association with the plasma film was obvious) and putative caveolae (vesicular profiles < 100 nm near the plasma layer however with no unmistakable association with the plasma film) per cell profile was included in 12 cell profiles for every condition, from two unique region of the way of life dish.

Western blotting assay

Equivalent measures of protein from cell lysates were electrophoresed in a 11% SDS-PAGE gel and moved to a nitrocellulose film. The proteins of interest were distinguished utilizing hare against caveolin-1 polyclonal neutralizer (1:1000) or bunny hostile to CAVIN1 polyclonal immune response (1:1000) trailed by auxiliary counter acting agent (1:10 000), recognized utilizing SuperSignal™ West Dura Extended Duration Substrate (Life Technologies) and evaluated utilizing a ChemiDoc™ Touch Imaging System (Bio-Rad).

Cell invasion assay

The cell attack examine was performed utilizing either CultreCoat® 24-well plates with BME-Coated Inserts or CultreCoat® 96 Well Medium BME Cell Invasion measure as already described¹²; the upper and base chambers had a similar centralization of NaCl added.

mRNA expression and survival analysis from publicly available data

AQP-1 mRNA articulation in typical mind tissues and different GBM atomic subtypes was recovered from Project Betastasis web stage (<http://www.betastasis.com>). Information were separated from The Cancer Genome Atlas (TCGA) consortium utilizing Affymetrix Human Exon 1.0 ST stage. The four sub-atomic subtypes of GBM (old style, mesenchymal, neural or proneural) were characterized in light of quality articulation profiles¹⁶ and have importance for endurance result or treatment reaction. For the endurance investigation, AQP-1 mRNA articulation utilizing U133 microarray and endurance information was removed from glioblastoma multiforme (TCGA, Firehorse Legacy), got to through CBioPortal.^{17,18} The Kaplan-Meier bends, log-rank test and Cox multivariable relapse examination were created utilizing GraphPad Prism (adaptation 8.01).

Measurable analysis | 2.14 Statistical examination was completed utilizing GraphPad Prism programming (v. 8.01). P-worth of a slight increment (around 2-overlap) in mRNA of CAV1 and CAVIN1 in the U251 cell line. A comparable pattern was found in the U87 and U118 cell lines for CAV1 mRNA, yet non-genuinely huge, and for CAVIN1 in U118 cells. Of note, the U118 cell line unexpectedly needs articulation of these two proteins fundamental for caveola formation.¹² CAV1 and CAVIN1 protein articulation was tried after hatching of the U87 and U251 cell lines in

charge and hyperosmolar media (Figure 1B), and a genuinely huge increment of the two proteins was seen in both cell lines (Figure 1C). Caveola measurement was performed on electron micrographs of U251 cells presented to control or hyperosmolar mechanism for 48 hours (Figure 1D). Hyperosmolality brought about a critical expansion in the quantity of caveolae, while the quantity of clathrin-covered pits was unaltered.

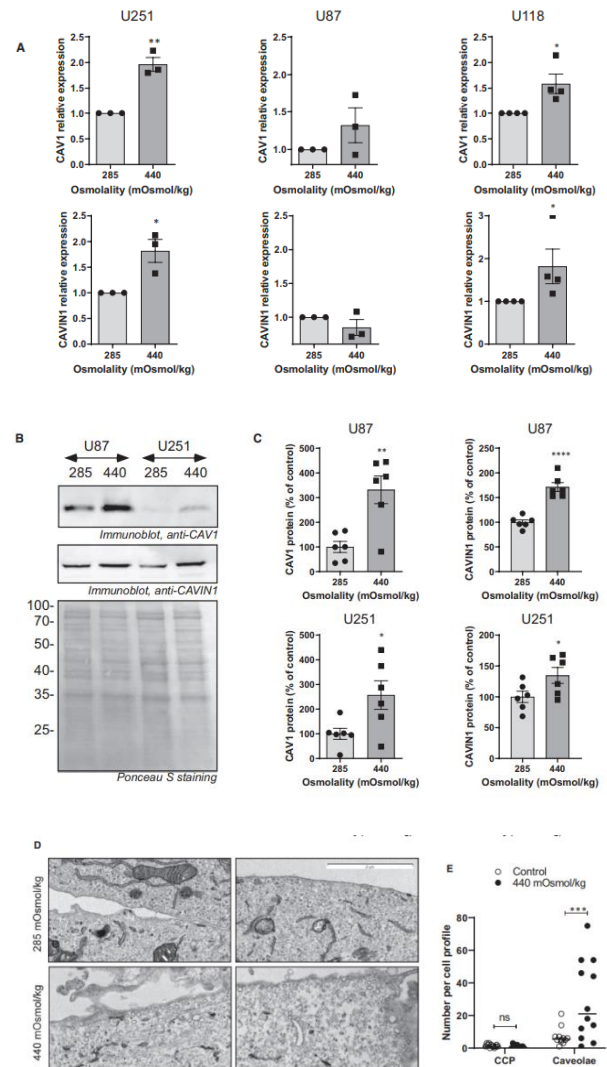
RESULTS

Osmotic pressure increases caveola-forming protein expression

We have recently exhibited that the declaration of caveolin-1 and CAVIN1 connects with GBM obtrusiveness¹² and that GBM cells react to osmotic tension by expanded creation of grid corrupting compounds, EMT markers and invasion.¹⁹ We found out if caveolae might be engaged with the cell reaction to pressure. We tried the mRNA articulation of CAV1 and CAVIN1 in GBM cells presented to hyperosmotic or hypo-osmotic mode for 48 hours (Figure 1A). The osmolality was changed by adding sodium chloride as already described.¹⁹ Hyperosmolality (440 mOsmol/kg) caused a slight increment (around 2-crease) in mRNA of CAV1 and CAVIN1 in the U251 cell line. A comparable pattern was found in the U87 and U118 cell lines for CAV1 mRNA, but non-genuinely critical, and for CAVIN1 in U118 cells. Of note, the U118 cell line suddenly needs articulation of these two proteins fundamental for caveola formation.¹² CAV1 and CAVIN1 protein articulation was tried after brooding of the U87 and U251 cell lines in charge and hyperosmolar media (Figure 1B), and a genuinely critical increment of the two proteins was seen in both cell lines (Figure 1C). Caveola measurement was performed on electron micrographs of U251 cells presented to control or hyperosmolar mechanism for 48 hours (Figure 1D). Hyperosmolality brought about a critical expansion in the quantity of caveolae, while the quantity of clathrin-covered pits was unaltered.

Osmotic strain increments caveola-shaping protein articulation. Cells were exposed to normo-(285 mOsmol/kg) or FIGURE 1 hyper (440 mOsmol/kg)-osmolar medium. (A) Effect of osmotic strain on CAV1 and CAVIN1 mRNA articulation among U251, U87 and U118 cell lines. Results are communicated as mean \pm SEM of $n = 3$ free investigations and examined utilizing unpaired one-followed t test. (B) Effect of osmotic strain on CAV1 and CAVIN1 protein articulation in U87 and U251 cell lines identified by immunoblotting. (C) Results of densitometric quantitation are displayed as a % of control osmolality. Results are communicated as mean \pm SEM of $n = 6$ judgments and investigated utilizing unpaired one-followed t test. (D) Representative electron micrographs of U251 cells presented to iso-(285 mOsmol/kg) or hyper (440 mOsmol/kg)-

osmolar mode for 48 h (E) measurement of clathrin-covered pits (CCP) and caveolae in 12 cell profiles for every condition. Results were broke down by single direction ANOVA with Dunnett's numerous examinations test or two-way ANOVA with Sidak's various correlation test. * $P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$

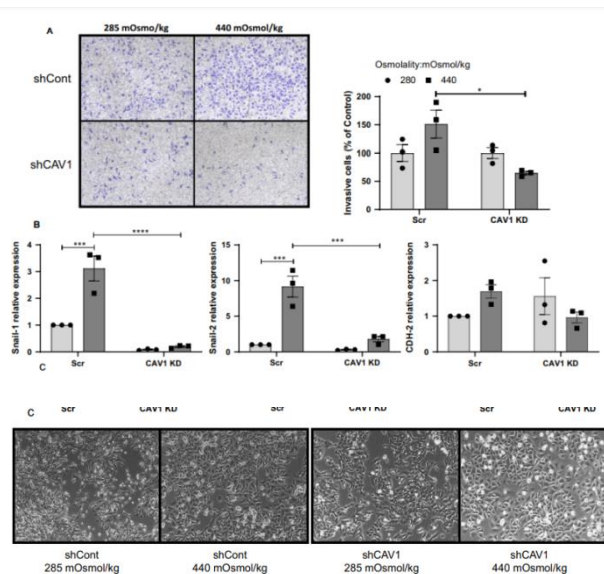


Caveolae are required for GBM pro-invasive response to hyperosmotic pressure

We surveyed whether caveolae are needed for the favorable to obtrusive reaction to tension by measuring uPA, gelatinase and EMT marker articulation in U251 cells in which CAV1 articulation was steadily downregulated by shRNA.¹² The phones were exposed to hyperosmolarity (360 and 440 mOsmol/kg) or hypo-osmolarity (260 mOsmol/kg) and contrasted with cells set in normo-osmolar (285 mOsmol/kg) medium. CAV1 down-guideline didn't influence the expanded creation of uPA because of 360 or 440 mOsmol/kg (Figure 2A) as was clear from casein-plasminogen zymography results. Moreover, no increment in MMP-2 was seen, and MMP-9 was undetected by gelatin zymography in one or the other control (scramble shRNA) or CAV1 down-managed cells (Figure 2B).

Be that as it may, uPA mRNA was altogether expanded in 440 mOsmol/kg medium (Figure 2C) and this reaction was dulled in CAV1 thumped down cells. MMP-2 mRNA was not expanded because of tension, and MMP-9 mRNA was expanded similarly in charge and CAV1 thumped down cells (ie 10-15 crease, no genuinely critical distinction; Figure 2C).

Impact of osmotic tension on grid protease creation of U251 cells steadily communicating shRNA to CAV1 (shCAV1) or FIGURE 2 control shRNA (shCont). Cells were exposed to normo-(285 mOsmol/kg), hyper-(360 or 440 mOsmol/kg) or hypo (260 mOsmol/kg)- osmolar medium. (A) Conditioned media of U251 shCont and shCAV1 cells presented to osmotic pressure were broke down by casein-plasminogen zymography and densitometric quantitation of the 47 and 51 kD groups comparing to uPA was done. (B) Gelatin zymography and densitometric quantitation of MMP-2 created in the adapted mechanism of U251 shCont and shCAV1 cells after 48 h of osmotic pressure. (C) Effect of osmotic weight on uPA, MMP-2 and MMP-9 mRNA articulation. Results are shown comparative with shCont. All outcomes are communicated as mean \pm SEM of $n = 3$ autonomous examinations. Densitometric measurement of uPA and MMP-2 was broke down by single direction ANOVA with Dunnett's numerous correlations test; protease mRNA articulation was investigated by two-way ANOVA with Tukey's various examinations test. * $P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$.



Caveolae are required for GBM pro-invasive response to hydrostatic pressure

Past work has shown that GBM react to hydrostatic tension by expanding framework proteases and EMT marker expression,¹⁹ and caveolae have been proposed to serve mechanosensing jobs. Along these lines, in the accompanying arrangement of trials, we evaluated whether CRISPR removal of caveola-shaping proteins CAV1 or CAVIN1 adjusted the supportive of obtrusive reaction of U251 cells to hydrostatic tension, that is 30 mm Hg applied to the

cells more than 48 hours, as beforehand described.¹⁹ The mRNA articulation of network proteases (Figure S6a,c) and EMT markers (Figure S6b,d) because of expanded hydrostatic strain was altogether lower in cells lacking caveola-framing proteins CAV1 or CAVIN1 for most of the qualities surveyed.

DISCUSSION

Our outcomes show that caveolae intercede, basically to some degree, the supportive of intrusive reaction of GBM to osmotic and hydrostatic tension. It has been shown evidently that the shortfall of the key caveola-framing proteins CAV1 or CAVIN1 forestalls the arrangement of caveolae. Caveolae shield cells from mechanical pressure by means of a mix of components; they give a film supply which can be conveyed when caveolae dismantle, level and cushion strains happening, for instance, in myofibre lengthening, and in light of hypo-osmotic stress, haemodynamic powers or tie pulling. It is likewise suggested that caveolae intercede the disguise of harmed layer areas. Lastly, the dismantling and smoothing of caveolae because of layer stretch permits the arrival of cavins to flag intracellularly (remembering for the core).

In the current review, we didn't notice significant impacts of hypo-osmotic treatment on framework protease creation or EMT marker articulation. Hypo-osmotic pressure has been involved at different forces for restricted measures of time in other reported investigations testing the job of caveolae in mechano-protection. These trials divulged a physiological job for caveolae in restricting layer strain because of cell stretch or expanding 22 and an expanded defenselessness to hypo-osmotic pressure and impeded film honesty in CAVIN1-/- muscle fibres.⁷ Hypo-osmotic medium was made by weakening DMEM 10-crease with 10% FBS-containing water,²³ applying hypo-osmotic medium at 30 mOsm rather than 300mOsm 6 and applying a HEPES-based arrangement at 180 mOsm versus isosmotic 280 mOsm.²² Durations were 10-15 minutes. In the current review, hypo-osmotic medium was applied for a significantly longer length (48 hours) and at a power viable with cell endurance (tried by MTT). This is a significant contrast with existing distributed work where fast cell expanding was utilized.

CONCLUSION

There is expanding proof that caveolin-1 and caveolae play numerous flagging and dealing with capacities GBM denoting this organelle or potentially its characterizing protein as focuses for a sickness that frantically needs clever restorative choices. Caveolae have been investigated as medication conveyance courses, and on the grounds that GBM's caveolae may be utilized to advance endocytosis of material with possible

remedial worth to cells (eg, pharmacological specialists and hereditary material). Shown take-up of remedial siRNA dendriplexes in GBM cells gives promising verification of idea to this methodology. What's more, the caveolin-1 inhibitory impact on P-gp can possibly expand drug conveyance to GBM cells by means of activity on the carrier at the BBB and GBM cell levels.

Both expanding and diminishing caveolin-1 articulation have been proposed as disease remedial approaches, utilizing ectopic articulation of caveolin-1 or siRNA, individually. In GBM, caveolin-1 overexpression rather than downregulation instigated a decrease in expansion, clonogenicity, and migration. This might appear to be illogical, as caveolin-1 is accounted for to be overexpressed in GBM contrasted and typical astrocytes. Nonetheless, caveolin-1 applies numerous impacts (direct hindrance, receptor endocytosis from cell surface, and compartmentalization) on various flagging pathways key to GBM development and attack. One more method for exploiting caveolin-1 tonic restraint on flagging atoms that has demonstrated to be successful in vivo is to mirror the inhibitory impact by utilizing the caveolin-1 platform space peptide, melded to a disguise arrangement permitting cell uptake.¹⁰¹ Although at first intended to control nitric oxide creation in endothelial cells, this peptide, named cavtratin, was displayed to stifle nerve development consider actuated MAPK enactment oligodendrocytes, showing that hindrance of development factor receptors can be accomplished in macroglial cells. Mutations of explicit amino acids in the framework area peptide can irritate, as opposed to recreating, the connection with target flagging molecules, and albeit this has been turned out for the collaboration of caveolin-1 with eNOS, the idea could be applied to produce peptides influencing development factor receptor hindrance. Ultimately, an aberrant technique to adjust caveolin-1 articulation and caveolae work is to impede cholesterol homeostasis with utilization of statins. Of interest, simvastatin diminished caveolin-1 articulation and decreased EGFR phosphorylation in astrocytes.⁸¹ It is probable that caveolin-1 will be assessed as an objective in GBM sooner rather than later, alone or in blend with presently accessible treatments to build their viability.

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