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REVIEW

Nano-Drug Delivery Systems Targeting MMPs: A Promising Treatment for Gliomas

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Abstract: Gliomas are the most prevalent Central Nervous System (CNS) tumors. Among them, glioblastoma (grade IV) is the most challenging brain cancer because of its highly aggressive nature, treatment resistance and poor prognosis. Matrix metalloproteinase (MMP) is a family of zinc-dependent protein hydrolases. In recent years, MMPs have become a research focus owing to their central role in tumor microenvironment remodeling, angiogenesis, invasion, metastasis. Clinical studies have shown that the expression levels of MMPs in glioma tissues exhibit a significant positive correlation with the degree of malignancy and aggressiveness of gliomas. Therefore, the idea of MMPs as a detection target and therapeutic target can be proposed. Nanoparticle drug delivery system, as a cutting-edge technology, has shown great potential and broad prospects in clinical applications. The system realizes the targeted delivery, sustained-release control and bioavailability of drugs, and provides new ideas and means for the management of various pathological conditions. In this review, we will comprehensively discuss the expression relationship and major regulatory mechanisms between MMPs and gliomas, the composition of nano-drug delivery systems, routes of administration, and common types of nanomaterials used for the treatment of gliomas. In addition, we focus on cell-penetrating peptides (CPPs) as an entry point. We summarize the common kinds of activatable CPPs and how they are applied in nano-drug delivery systems. It is also found that MMP-responsive systems, which can be used for the treatment of gliomas, can activate CPPs, and through the synergistic effect between CPPs and MMPs, MMPs can be used as detection or therapeutic targets and combined with nano-drug delivery system for the medical management of gliomas. The nano-drug delivery system can demonstrate exceptional blood-brain barrier (BBB) penetration efficiency and precisely target the glioma region to release the drug. This delivery approach may prove to be beneficial for glioma patients.

Keywords: matrix metalloproteinase, glioblastoma, nanomaterial, cell-penetrating peptides, nano-drug delivery systems

Introduction

Gliomas are the most prevalent central nervous system tumors. Among these malignancies, glioblastoma (GBM) represents the most formidable brain cancer due to its highly aggressive nature, treatment resistance, and extremely poor prognosis. Treatment options include maximal surgical resection, postoperative radiation therapy with temozolomide and chemotherapy.[1,2] GBM has a high rate of postoperative recurrence because of its very invasive nature, which makes it difficult for surgeons to assess whether the tumor has been entirely removed.[3,4] Despite aggressive treatment strategies, overall survival in GBM remains poor due to tumor heterogeneity, BBB-related drug delivery barriers, and therapy resistance. This mainly stems from the heterogeneity of the tumor, the BBB, limitations on drug penetration, and drug resistance of the tumor cells.[5–7] GBM is the most harmful brain cancer for two reasons. Firstly, the tumor usually grows invasively, and complete surgical resection is difficult to achieve.[8] Secondly, the BBB prevents the majority of antitumor agents from effectively targeting tumor sites.[9–11] Given these challenges, emerging therapeutic approaches such as nanotechnology-based drug delivery systems have gained attention. These systems can be engineered to bypass the BBB and deliver therapeutic agents specifically to the glioma microenvironment, particularly by targeting over-expressed molecules like MMPs.

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Due to the specific expression of MMP in tumors, it has been used to target various tumors with anti-cancer drugs, enabling precise drug delivery. Moreover, with the recent rise of nano-drug delivery systems, their tiny nanoscale size allows drugs to easily penetrate the blood-brain barrier and deliver drugs more effectively. Many studies have combined these two approaches to address the challenges of drug treatment for gliomas, making drug delivery more precise and efficient to the tumor site. However, there are still obvious knowledge gaps in the field: first, the expression differences of different MMP subtypes in gliomas and their correlation with the targeting mechanism of nano-drug delivery systems have not been systematically analyzed; second, for MMP-targeted nano-drug delivery systems, there is a lack of comprehensive integrated analysis on the selection of nanomaterials, targeted modification strategies, and administration routes; third, key bottlenecks in clinical translation—such as targeting accuracy issues caused by the heterogeneity of MMP expression and potential toxicity of nanocarriers—have not been clarified. By summarizing the research progress in recent years, this review addresses the above issues and discusses the feasibility of MMP-targeted nano-drug delivery systems in the treatment of gliomas.

MMP Classification and Expression Relationship in Gliomas

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that degrade components of the extracellular matrix and modulate signaling pathways, thereby influencing tumor invasion, angiogenesis, and metastasis. It is involved in various physiopathological processes and has a significant impact on tumorigenesis and development.[12–15] Currently, the MMP family consists of approximately 24 members (eg, MMP-2, -9, -14, etc.), which, once activated, are precisely regulated by a series of endogenous tissue inhibitors, such as TIMP-1 and TIMP-2.[16] It has been shown that in some instances, the expression of MMP family members is positively correlated with the stage of tumor progression. Furthermore changes in MMP levels significantly affect the invasiveness and metastatic potential of cancer cells.[17] Specifically, MMPs are able to degrade various structural components in the extracellular matrix, such as collagen and fibronectin, to regulate tumor cell invasion and migration. In particular, by cleaving laminin-5, transforming growth factor β (TGF-β), interleukin-6 receptor (IL-6R), and tumor necrosis factor (TNF),[18,19] the integrity of the (ECM) is disrupted, the physical barriers to cellular motility are removed, and the pathways to invading cells are created.[20] Besides degrading the extracellular matrix (ECM), MMPs also promote angiogenesis. MMPs are involved in neovascularization by enhancing the mobility of endothelial cells and increasing the release of pro-angiogenic factors. In turn, neovascularization provides tumors with the required oxygen and nutrients to support their growth and spread (Figure 1).[21,22] Furthermore, MMPs can modulate the growth of tumor cells by altering the signaling pathways associated with cell proliferation and apoptosis.[23] For example, MMP-2 regulates IL-6/Stat3 survival signaling by interacting with α5β1 integrin in gliomas, thereby enhancing tumor cell proliferation.[24–26] Thus, MMPs can affect the tumor environment by degrading the ECM, promoting angiogenesis, tumor growth and metastasis.[21,27,28]

In addition to being categorized into secreted MMPs and anchored MMPs (MMP-14, -15, -16, etc.),[29,30] MMPs are commonly categorized into seven primary groups according to their in vitro substrate specificity: (1) Interstitial collagenases that cleave type I–III interstitial collagen include MMP-1, -8, -13, and -18; (2) Gelatinases (MMP-2 and -9) that break down basement membrane proteins and denatured collagen (gelatin); (3) Matrix hemolysins (MMP-3, -10, and -11) break basement membrane proteins, including laminin; (4) Membrane-type MMP (MT-MMP), which is expressed on the cell surface and linked to the plasma membrane by transmembrane structural domains (MMP-14, -15, -16, and -24) or glycophosphatidylinositol anchors (MMP-17 and -25); (5) Matrix cleavage proteins (MMP-7 and -26) cleave proteoglycans, laminin, elastin, and type IV collagen. They do not have a carboxy-terminal structural domain; (6) Metalloelastase (MMP-12), which breaks down some basement membrane proteins and elastin; (7) Other MMPs (MMP-19, -20, -23 and -28) (Table 1).[31] Among them, patients with malignant tumors had considerably higher serum levels of MMP-2 and -9, which may be positively correlated with poor prognosis. Moreover, the degree of their expression is important for the recurrence of gliomas. Studies have demonstrated that recurrent gliomas exhibit markedly elevated levels of MMP-2 and MMP-9 compared to primary gliomas. Additionally, high expression of metalloproteinases (especially MMP-9 and -2) has been detected in malignant brain tumors.[32,33] Therefore, MMP-2 and -9 may serve as potential targets in the management of gliomas.

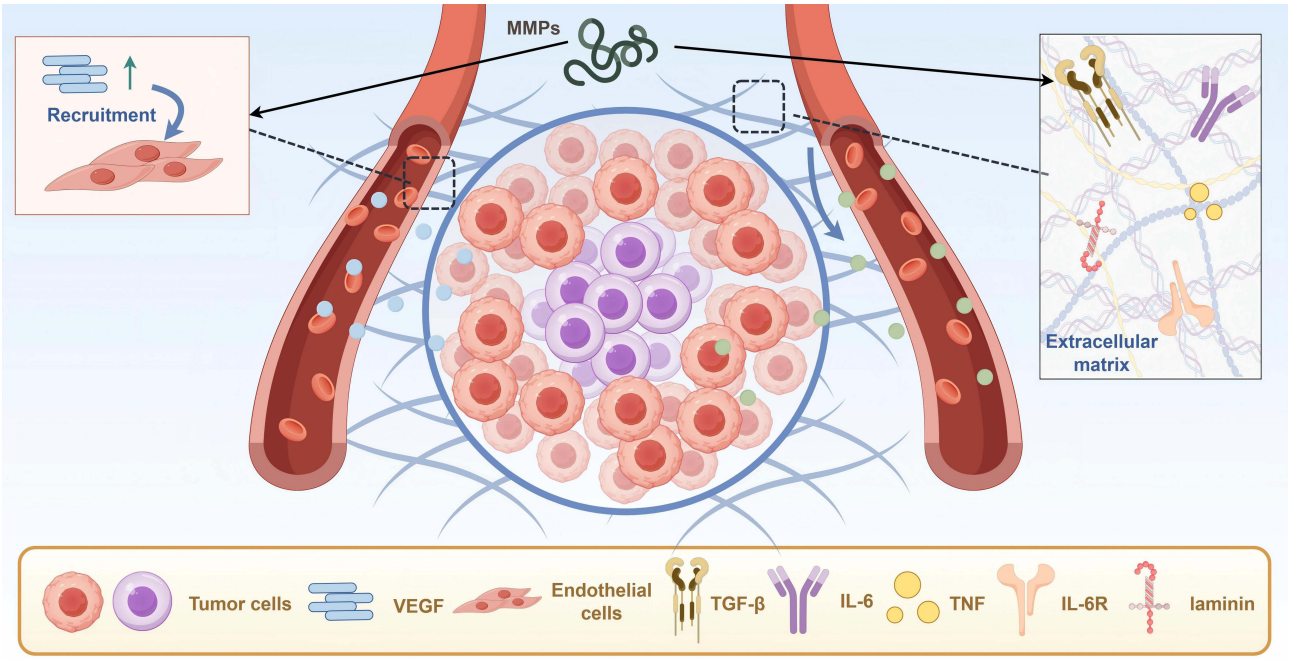

Figure 1 The role of MMPs in tumor cell invasion and metastasis. MMPs play a crucial role in the tumor process. On the one hand, they eliminate the physical barriers to cell movement by degrading components in the ECM and cleaving various factors, such as IL-6R and TNF, thus clearing the way for tumor cell invasion. On the other hand, MMPs can promote angiogenesis by enhancing endothelial cell mobility and increasing the release of pro-angiogenic factors, thereby creating conditions for the formation of tumor neovascularization (By Figdraw).

Since MMPs can degrade ECM and disrupt its barrier function, this is conducive to the invasion and metastasis of glioma cells. Therefore, high expression of MMPs enhances the invasive ability of glioma cells,[32,53,54] making them more likely to invade and spread to surrounding tissues.

In addition, as the grade of glioma increases, the expression level of MMPs will also increase accordingly. Statistical analysis demonstrated a significant positive association between MMP-2 and MMP-9 expression levels and the histological grade in primary and recurrent gliomas. Studies have indicated that MMP-2 and MMP-9 act synergistically to promote tumor progression.[32] It was also experimentally found that the expression of MMP-1, MMP-9, MMP-11, and MMP-19 in GBM was enhanced in terms of signal intensity and the percentage of tumors displaying MMP expression compared to low-grade astrocytoma (LGA) or normal brain (NB). In addition, compared to LGA or NB, MMP-9 expression was significantly increased in GBM at both mRNA and protein levels. Moreover, all GBM cases exhibited MMP-9 protein expression, suggesting the innate relevance of MMP-9 to tumor malignancy.[55]

Although it has been shown that the degree of MMP expression is positively correlated with the malignancy and aggressiveness of gliomas, the specific molecular mechanism underlying this relationship remains to be further elucidated. Through in-depth study of the expression patterns of MMPs and regulatory networks in gliomas with different degrees of malignancy, we can more accurately assess the risk of tumor progression in patients and design more precise and effective individualized treatment plans accordingly. This will not only help to enhance therapeutic efficacy, but also reduce over-treatment (ie, administering more intensive therapy than necessary) of patients and improve their quality of life.

Regulatory Mechanisms of MMP Modulation in Brain Gliomas

Regulatory Mechanisms at the Level of Transcription

The regulatory mechanisms at the level of transcription between MMPs and gliomas in humans are complex and involve multiple signaling pathways, as shown in Figure 2.

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Table 1 Classification of MMPs

Categorization	Example	Gene Localization	Primary Substrate	Primary Expression Organization	Physiological Function	Pathological Function	References
Interstitial collagenases	MMP-1	11q22.2–22.3	Collagen (I, II, III, VII, VIII, X)	Fibroblasts, macrophages, endothelial cells and epithelial cells	Development, tissue morphogenesis and wound repair	Arthritis, pulmonary fibrosis, cancer	[34–37]
	MMP-8	11q22.3	Collagen (I–III, V, VII, VIII, X)	Chondrocytes, endothelial cells, macrophages, smooth muscle cells	Anti-inflammatory activity	Periodontitis, rheumatoid arthritis	[37–40]
	MMP13	11q22.3	Gelatin, collagen (IV–VI, X)	Cartilage, bone, epithelial cells, neuronal cells	Osteoclast activation, anti-inflammatory activity	Osteoarthritis, cancer	[35–38,41]
	MMP-18	12q14	Collagen (I, II, III)	Expressed in normal human tissues but not detected in brain, skeletal muscle, kidney, liver or leukocytes	Axonal growth	Not directly related to a specific pathological condition	[37,42]
Gelatinases	MMP-2	16q13	Gelatin, collagen (IV, V, VII, X, XIV)	Endothelial cells, cardiomyocytes, fibroblasts	Neovascularization, promotion and suppression of inflammation	Cancer, asthma, lung disease	[35–38,43,44]
	MMP-9	20q11.2-q13.1	Gelatin, collagen (IV, V, VII, X, XIV)	Endothelial cells, neutrophils, eosinophils	Wound healing, neovascularization, tissue remodeling, immune cell function	Arthritis, lung disease, cardiovascular disease	[35–38,43]
Matrix hemolysins	MMP-3	11q23	Laminin, aggregated proteoglycan, gelatin; fibronectin	Fibroblasts, macrophages	Promotes fibroblast wound healing and repairs dentin formation	Arthritis, atherosclerosis	[37,42,44,45]
	MMP-10	11q22.3-q23	Collagen (III–V), gelatin	Keratinocyte	Liver regeneration, bone development, wound healing, vascular remodeling	Idiopathic pulmonary fibrosis, tumor metastasis	[37,42,44,46,47]
	MMP-11	22q11.2	Fibronectin, laminin, aggregated proteoglycan, gelatin	Fibroblast-like cells, adipocytes	Embryo implantation, individual organ development, tissue degeneration, and repair processes	Breast cancer, atherosclerosis, rheumatoid arthritis	[37,42,44,48]
Matrix cleavage proteins	MMP-7	11q21-q22	Collagen (IV–X), fibronectin, laminin, gelatin	Mucous membrane epithelial tissue	Remodeling of developmental and reproductive tissues	Idiopathic pulmonary fibrosis, carcinogenesis and metastasis	[37,42,44,47]
	MMP-26	11p15	Gelatin, collagen IV	Expressed in normal cells of epithelial origin as well as in specific cancers including endometrial, breast and prostate cancers	Involved in skin and intestinal wound repair	Non-small cell lung cancer, breast cancer	[37,42,44,49–52]
Metalloelastase	MMP-12	11q22.2-q22.3	Elastin, gelatin, collagen types I and IV, fibronectin, laminin	Neutrophils, endothelial cells, T cells, fibroblasts, macrophages, myocytes	Degradation of extracellular matrix components	Arthritis, emphysema, periodontal disease, cancer	[37,38,44]

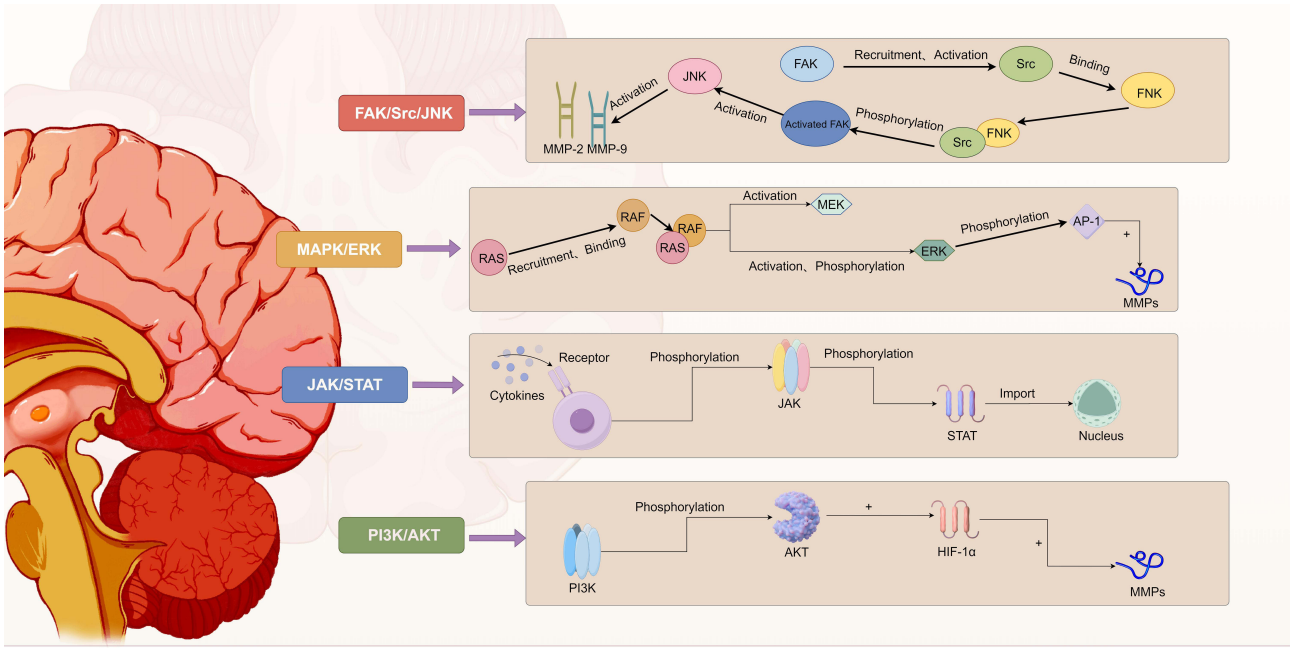

Figure 2 The main regulatory mechanisms at the transcriptional level between MMP and glioma. The transcriptional regulation of MMPs in glioma involves multiple complex signaling pathways. The FAK/Src/JNK axis begins with FAK recruiting and activating Src, followed by FNK binding to Src to form a complex, phosphorylating FAK and activating JNK, thereby promoting the activation of MMP-9 and MMP-2. The MAPK/ERK pathway starts with RAS activation, which successively activates RAF, MEK and ERK, and finally activates MMPs via phosphorylated ERK. In the JAK/STAT pathway, the binding of cytokines to receptors successively activates JAK and STAT, after which phosphorylated STAT enters the nucleus to regulate transcription. In the PI3K/AKT pathway, PI3K phosphorylates AKT, enhancing the activity of HIF-1α and thereby increasing the expression of MMPs (By Figdraw).

FAK/Src/JNK Axis

The focal adhesion kinase (FAK) signaling pathway is initiated by FAK-mediated recruitment and activation of Src, after which FNK binds to Src to form a complex that induces FAK phosphorylation and activation.[56–58] Subsequently, downstream c-Jun N-terminal kinase (JNK) is activated, thereby inducing MMP-2 activation and facilitating MMP-9 secretion.[59] PPFIA binding protein 1 (PPFIBP1) is a ubiquitously expressed protein in the human body that exhibits significant associations with the tumorigenesis and progression of multiple malignancies. The degree of PPFIBP1 expression in gliomas has been found to be positively correlated with the degree of tumor invasion. The upregulation of PPFIBP1 may enhance glial tumor cell migration and invasiveness by promoting FAK signaling through interactions with SRCIN1 and enhancing MMP-2 expression through the FAK/Src/JNK axis.[60]

MAPK/ERK Pathway

Mitogen-activated protein kinase (MAPK) pathway is closely related to tumor development. It starts with the activation of RAS, which then recruits and binds to RAF downstream to activate RAF, followed by the activation of MEK and ERK, and finally the activation of other downstream substrates by phosphorylated ERK.[61,62] ERK promotes the phosphorylation of downstream AP-1 and enhances its activity. Many MMPs, such as MMP-2, -3, and -9, contain one or more AP-1 binding sites in their promoters, and the activation of AP-1 promotes the expression of MMPs.[63] Many tumors promote their own invasion by regulating MMP secretion from fibroblasts, which are not present in the brain. It has been found that gliomas promote MMP secretion from astrocytes via CD147 in their extracellular vesicles, which in turn promotes invasion. This process is likely mediated by the MAPK pathway.[64]

JAK/STAT Pathway

The main process of this pathway is that cytokines bind to extracellular membrane receptors and transmit signals to Janus Kinase (JAK), which is activated by phosphorylation. The phosphorylated JAK then further phosphorylates the downstream signal transducer and activator of transcription (STAT), and the phosphorylated STATs enter the nucleus as part of the transcription factors and play a role in transcriptional regulation.[65,66] STAT3 binds to the promoter of

MMP-2, upregulates MMP-2 transcription and promotes its expression.[67] Migfilin also known as Filamin-Binding Lim Protein 1 (FBLIM1) is distributed in the heart, lungs, intestine and uterus. It is involved in cell adhesion, shape regulation, motility and transcriptional regulation, and is a key extracellular and intracellular signal transducer. Previous studies have demonstrated that this protein triggers MMP-2 activation and stimulates glioma invasion by binding to and activating epidermal growth factor receptor (EGFR), as well as initiating STAT3 and phospho-lipase C-γ (PLC-γ) signaling.[68]

PI3K/AKT Pathway

The main process of this pathway is that Phosphatidylinositol 3-kinase (PI3K) is activated under hypoxia conditions, and then binds to and phosphorylates downstream AKT. Phosphorylated AKT enhances the activity of hypoxia-inducible factor-1α (HIF-1α) to control cell proliferation.[69] The expression of MMPs is intimately associated with HIF-1α, which upregulates the expression ofMMPs, thereby enhancing the invasive potential and metastatic dissemination of solid malignancies.[70] Small transmembrane and glycosylated protein (SMAGP) is a novel small transmembrane glycoprotein. It is highly conserved during evolution and highly expressed in many tumors, including gliomas. Studies have shown that SMAGP indirectly affects MMP expression in gliomas through the PI3K/AKT pathway, which in turn promotes glioma invasion.[71] Meanwhile, it has been found that demethoxycurcumin (DMC) can reduce glioblastoma invasion by inhibiting the PI3K/AKT pathway.[72]

In summary, we found that the FAK/Src/JNK axis, the MAPK pathway, the EGFR/STAT3 pathway and the PI3K/AKT pathway play important roles in the genesis and development of gliomas. However, these pathways are not completely independent of each other, but are interconnected. For example, in addition to phosphorylating STAT to transmit signals, JAK in the JAK/STAT signaling pathway can also activate the MAPK and PI3K/AKT signaling pathways by bypassing phosphorylation of SHP2 and PI3K. Consequently, targeting a single signaling pathway may fail to achieve the desired clinical outcomes. Perhaps, targeting key interconnected nodes in multiple signaling pathways, such as JAK mentioned above, may be more effective. In the future, we may more effectively inhibit the growth and invasion of gliomas by exploring combined multi-pathway intervention strategies. This combination therapy is expected to be a novel therapeutic modality for the treatment of gliomas.

Regulatory Mechanisms at the TIMP Levels

Tissue Inhibitor of Metalloproteinases (TIMP) is a natural protein whose primary function is to regulate ECM degradation and reformation through binding to MMPs and inactivating their enzymatic functions. Through its regulation of MMPs, TIMP plays a crucial role in controlling tumor invasion and metastasis. TIMPs are mainly classified into four categories, TIMP-1, -2, -3 and -4, and their respective functions are different.[73]

TIMP-1

Although TIMP-1 has an inhibitory effect on MMPs, its expression level shows no positive correlation with glioma prognosis; moreover, gliomas with low TIMP-1 expression levels have a better prognosis.[74,75]

TIMP-2

In fact, there have been conflicting findings on the effects of TIMP-2 on cancer. For example, one study demonstrated that TIMP-2 expression was positively correlated with the recurrence of fibrosarcoma.[76] However, another study in mice with breast cancer showed that TIMP-2 plays a role in inhibiting tumor metastasis and growth.[77] This is mainly due to the differences in gene expression in different tumors, which in turn cause variations in the ECM's composition, ultimately altering the role of TIMP-2.[78] Studies in gliomas have shown that the elevated TIMP-2 did not inhibit MMP activities. In contrast, it caused MMP-2 activity to increase, which enhanced the aggressiveness of the tumor.[79] The specific mechanism for this aberrant expression may be the interaction of TIMP-2 with membrane type 1 matrix metalloproteinase (MT1-MMP), which triggers a pro-migratory ERK signaling cascade, leading to a non-negative correlation between TIMP-2 expression and the poor prognosis of gliomas.[76,80,81]

TIMP-3 and -4

The experimental results of TIMP-3 and -4 showed that their activities were positively correlated with glioma prognosis. They reduce the invasive function of gliomas by inhibiting the activity of MMPs thereby improving the prognosis of glioma patients. And there is also a significant positive correlation between their two expressions.[82]

In conclusion, the regulatory effect of MMPs at the level of TIMP in gliomas is influenced by a variety of factors. For example, distinct TIMP classes exhibit markedly divergent effects on glioma progression. TIMP generally acts as an intermediate mediator in the treatment of gliomas. Clinically, TIMP is more commonly used as a prognostic marker for gliomas.

The Application of MMPs in Gliomas

As a Diagnostic Marker

Since the high expression of MMP in gliomas is positively correlated with the degree of malignancy, it can be used as a potential diagnosis marker for gliomas. Detection of MMP levels in cerebrospinal fluid or serum can assist in the diagnosis of gliomas and assessment of their malignancy. For example, a study utilized Fluorescence Molecular Imaging (FMI) to perform targeted fluorescence imaging of in situ glioma with MMP-750, then reconstructed the Fluorescence Molecular Tomography (FMT) of MMP-750 to provide depth and volume metrics for in situ gliomas. This approach assisted in glioma diagnosis and enabled precise surgical resection.[83]

As a Prognostic Marker

Due to the highly aggressive nature of gliomas, the majority of patients with gliomas exhibit a poor prognosis. Therefore, monitoring the prognostic level is important. Precisely because MMPs are closely related to the aggressiveness of gliomas, MMP expression levels may serve as a robust predictive biomarker for clinical outcomes in glioma patients. Gliomas with high MMP expression are more aggressive and have a poorer prognosis. It has been found that in patients with recurrent gliomas, the expression of MMP-2 and -9 is significantly increased, which can be used as a marker for determining the prognosis of the tumor, and their elevated expression indicates a poor prognosis.[32]

As a Therapeutic Target

Since MMPs play important roles in the occurrence and development of gliomas, they have also become a potential candidate for targeted therapy. Suppression of MMP activity or expression effectively inhibits glioma cell invasion and metastasis, offering a viable strategy for glioma treatment. MMP-9 levels in glioma patients have been shown in multiple studies to significantly increase after radiation therapy. Knockdown of MMP-9 expression, however, significantly reduces radiation-induced invasion. Therefore, it may be able to serve as an important target for radiosensitization.[32] MicroRNAs (miRNAs) are a class of small, single-stranded, endogenous RNAs that do not code for proteins. They serve as important post-transcriptional regulators of gene expression. miRNA dysregulation is an important mechanism of brain glioma invasion and migration. As important targets of miRNAs, MMPs have been extensively studied in numerous investigations where various miRNAs were overexpressed to downregulate MMP expression. This approach subsequently inhibits glioma cell invasion and migration, thus facilitating glioma therapy.[84–87]

Nanomaterials Targeting MMPs

Components of Nano-Drug Delivery Systems

Nano-drug delivery systems primarily refer to a class of drug delivery systems that utilize nanotechnology for targeted therapeutic delivery. In addition to the specific therapeutic drug loaded inside, it consists of two main components. The first part is the nanoparticles used to load the drug. Different nanoparticles have different properties that make it easier for them to cross some biological membrane structures, such as the blood-brain barrier. The second part is the targeting element for achieving specificity. This section mainly consists of specific targeting molecules, such as peptides and antibodies, which enable the drug delivery system to precisely target the site of action (Figure 3). In conclusion, nano-

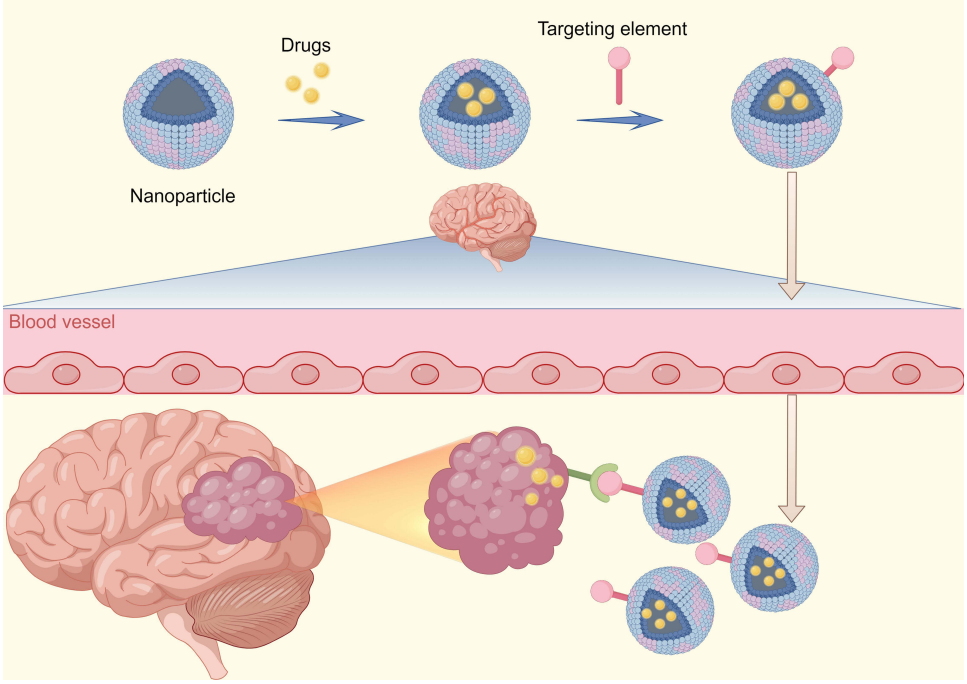

Figure 3 The composition of nano-drug delivery systems. The nano-drug delivery systems are composed of nanoparticle loaded with drugs and targeting element. The former helps drugs penetrate the BBB, while the latter precisely locates glioma lesions (By Figdraw).

drug delivery systems combine nanotechnology and targeting technology, which enables drugs to exert therapeutic effects more accurately and efficiently, and is a hot research topic in recent years (Figure 4).

Common Types of Nanomaterials Used in the Treatment of Brain Gliomas

In the research into treatment of glioma, nanomaterials show great potential. Multiple types of nanomaterials are widely studied to address this medical challenge. The following presents the applications of several common nanomaterials in glioma treatment (Table 2).

Lipid Nanoparticles

Liposomes and lipid nanoparticles (LNPs), the two primary structural subgroups of lipid nanoparticles, are created via self-assembly. Liposomes are frequently made of naturally occurring phospholipids and feature a lamellar vesicle structure. The most widely utilized liposomes for delivering nucleic acids are LNPs, which have micellar structures inside their core. In addition to this, liposomes offer a variety of advantages, including biocompatibility, self-assembly capability, large drug payload capacity, and wide-ranging physicochemical and biophysical properties, which can be engineered to modulate their biological behaviors. Liposomal formulations are defined by key physicochemical attributes, including charge, particle size, lipid composition, number of lamellae, and surface modification of polymers and ligands. These factors determine their stability both in vitro and in vivo. Furthermore, liposomal encapsulation serves as a protective barrier against early inactivation, degradation, and dilution in circulation.[112–115] Some experiments have shown that when curcumin (CUR) or palladin (PTN) is encapsulated in lipid nanoparticles using double asymmetric centrifugation, the formed lipid nanoparticles loaded with photosensitizers (PS) can be used for photodynamic glioblastoma therapy in vitro and in vivo.[116]

Polymer Nanoparticles

It is possible to create polymeric nanocarriers with a variety of structures and properties by synthesizing them from natural or artificial materials. Based on the structure of the nanoparticles, they can be divided into some subsets such as polymer bodies, micelles, and dendrimers. Polymer bodies are composed of amphiphilic block copolymers which form vesicle

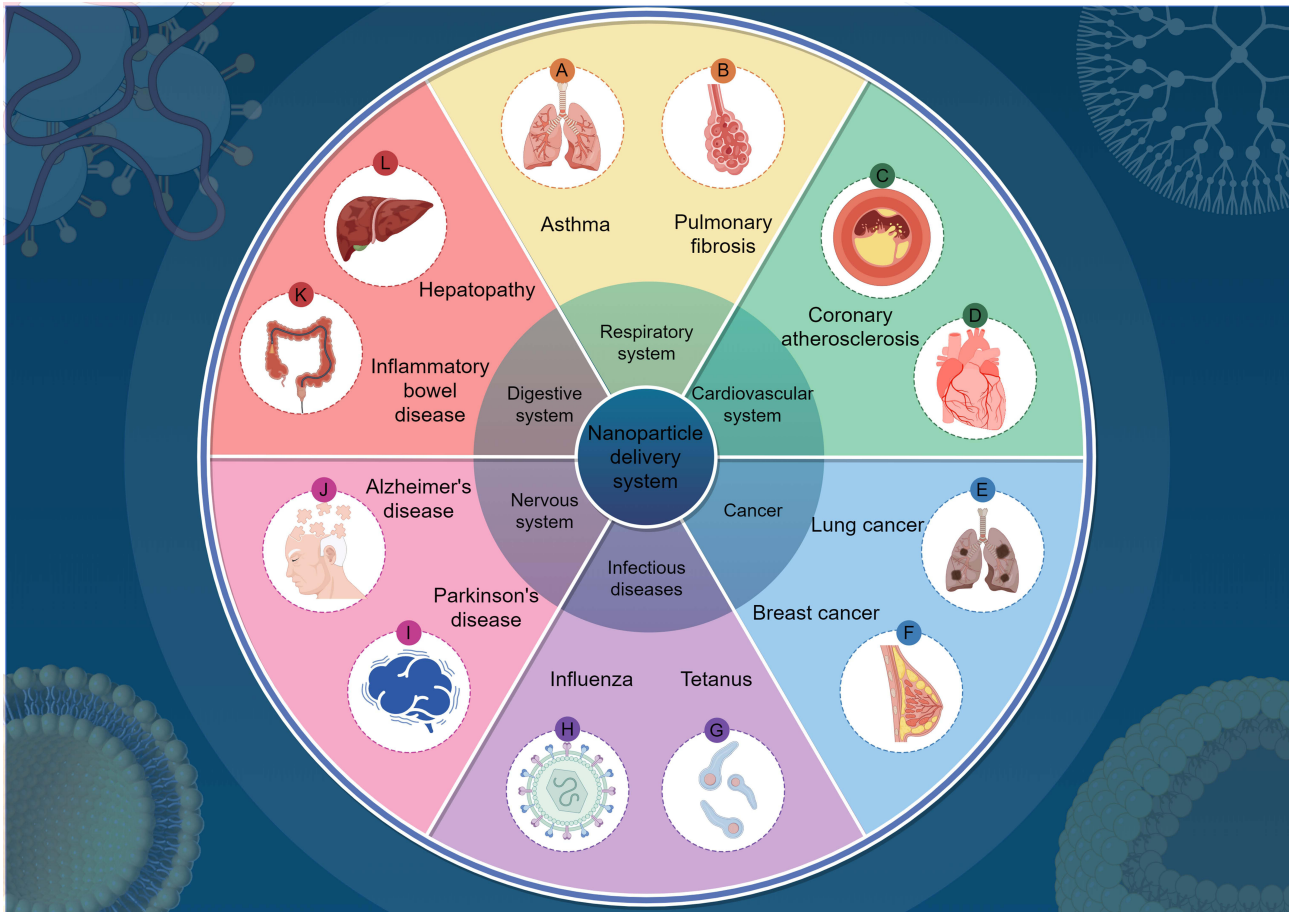

Figure 4 Clinical applications of nano-drug delivery systems. The figure illustrates the clinical applications of nano-drug delivery systems in the treatment of various diseases. These include respiratory diseases (pulmonary fibrosis and asthma), cardiovascular diseases (coronary atherosclerosis), cancers (breast and lung cancer), infectious diseases (influenza and tetanus), neurological diseases (Alzheimer's and Parkinson's disease), and digestive diseases (inflammatory bowel disease and hepatopathy). It reflects the broad potential of nano-drug delivery systems across diverse medical fields (By Figdraw).

structures analogous to those of liposomes. Polymer micelles are typically formed by amphiphilic block copolymers that spontaneously organize into spherical nanostructures with a separation between the hydrophilic nature of the inner core and that of the outer shell. In contrast, dendrimers are hyperbranched polymers that form three-dimensional structures with controllable shape, size, and charge.[112,117–120] Polymer nanoparticles offer several advantages, including the ability to tailor the physical, biological, and chemical properties of the nanocarriers. Such biodegradable polymers are favored by researchers because they break down under physiological conditions. This action typically achieves a dual effect: mitigating the potential toxicity of the macromolecule while enhancing drug release.[121–123] Caverzán et al[124] experimentally evaluated the efficacy of photodynamic therapy (PDT) mediated by an advanced photosensitizer (PS) synthesized from conjugated polymer nanoparticles (CPNs). These nanoparticles were analyzed under various irradiation conditions with different light fluence rates to evaluate the potential of CPNs as photocide in GBM cell lines. Finally they found that CPN slightly promoted apoptosis in GBM cells.

Inorganic Nanoparticles

Inorganic nanoparticles can serve as contrast agents for diagnostic procedures as well as medicine delivery systems.[112] Common types of inorganic nanoparticles include metal nanoparticles, oxide nanoparticles, phosphate nanoparticles and carbon nanoparticles. Among them, metal and metal oxide nanoparticles can be used for brain cancer treatment because of their small size and potential to break through the BBB. Compared to gold (Au NPs) and silver nanoparticles (Ag NPs), copper oxide nanoparticles (CuO NPs) are not only more cost-effective but also exhibit a potent killing impact on cancer cells due to the liberated copper ions. In an experimental study conducted by Tian et al.[125] CuO NPs treatment

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Table 2 Common Nanomaterials Used in the Treatment of Glioma

Common Types of Nanoparticles Used for the Treatment of Brain Gliomas	Material Composition	Physical Property	Advantages	Disadvantages	Applications in Cancer Therapy	References
Lipid nanoparticles	Ionizable lipids, co-lipids, cholesterol and polyethylene glycolated lipids	50–200 nm, spherical	Protection against enzymatic degradation, low toxicity, flexibility, biocompatibility, complete biodegradation and non-immunogenicity of drugs	Short shelf life, poor stability, low encapsulation efficiency	Bowel cancer, stomach cancer, breast cancer, etc.	[88–90]
Polymer nanoparticles	Natural polysaccharides (eg chitosan), synthetic polymers (eg PLGA) and surfactants (eg polyethylene glycol)	10–1000 nm, diverse morphology	Versatility, biocompatibility and ability to provide controlled release properties	Potential toxicity, stability issues, manufacturing complexity	Lung cancer, stomach cancer, breast cancer, etc.	[91–95]
Inorganic nanoparticles	Inorganic materials (magnetic metals, ceramics, semiconductors)	10–100 nm, diverse morphology	Good stability, easy surface functionalization, adjustable degradation rate	Adverse toxic effects (oxidative stress, inflammation and genotoxicity), low biodegradability, poor biocompatibility	Breast cancer, lung cancer, etc.	[94,96–99]
Dendritic polymers	Synthetic polymers (eg polyamide amines, etc)	1–100nm, dendritic	Stability, high load capacity	Toxic and complex to synthesize	Breast cancer, lung cancer, etc.	[100–105]
Exosome	Proteins, lipids and nucleic acids	30–150nm, spherical	Biocompatibility, biostability, high targeting, good biocompatibility, no immunogenicity	Complex separation, classification and purification processes	Lung cancer, melanoma, breast cancer, etc.	[105–111]

reduced the expression of MMP-9 biomarkers in glioma cells and model rats. Thus, CuO NPs have been demonstrated as novel potential glioma therapeutic agents.

Dendritic Polymers

Dendritic polymers are characterized by symmetrical, highly branched three-dimensional structures with strictly defined molecular weights. They are structurally similar to spheres. They typically have three main components: a peripheral group, a connecting bridge, and a central core. The ends of dendrimers can be covalently or non-covalently attached to bioactive molecules, drugs, genes, contrast agents and other reporter genomes.[101,126–128] Dendritic polymers not only have the advantage of high drug-carrying capacity, but can also be prepared in different sizes and modified so that their surfaces can carry ligands.[129] There are two approaches to using dendritic polymers for medication delivery: formulations encapsulated in dendritic macromolecules using non-covalent interactions; and nanostructures formed by covalently linking the drug to the dendritic polymer. Both approaches effectively improve the oral bioavailability, stability, and solubility of various medications.[130,131] Xiaowei Shi et al[132] designed and synthesized a dendritic macromolecule-mediated drug delivery system for targeted glioma therapy. This system increased the amount of drug crossing the BBB by combining nanocarriers and targeting techniques, which resulted in targeted drug accumulation and activation within the neoplastic tissue. This targeted delivery system demonstrates significant potential for precision therapy of gliomas.[132,133]

Exosome

Extracellular vesicles (EVs) are a heterogeneous class of lipid bilayer-enclosed particles that are naturally released from most human cells under physiological and pathological conditions. Their role in intercellular communication makes them a very important component of the tumor process. EVs are broadly classified into three categories based on different biogenesis pathways and sizes: apoptotic vesicles, microvesicles, and exosomes. Exosomes are a class of extracellular vesicles produced by endocytosis, with a diameter ranging from 30 to 150 nm.[134–137]

Exosomes enable donor cells to deliver exogenous substances including proteins, mRNAs, miRNAs, and lipids to recipient cells. Owing to their natural cargo-carrying capacity, these nanoscale vesicles have emerged as promising drug delivery vehicles. Compared to synthetic nanocarriers, patient-derived exosomes exhibit superior biocompatibility and reduced toxicity. Moreover, they demonstrate remarkable tissue penetration, efficient diffusion into the bloodstream, and the ability to cross the BBB.[106,138–140]

Li et al[141] proposed a unique composite treatment platform. This platform combines the siRNA encapsulation and BBB penetration ability of modified exosomes for GBM therapy with the magnetic targeting and drug delivery capabilities of magnetic nanoparticles. Under targeted magnetic localization, the platform can be enriched in the brain. Transcytosis can be triggered by designed exosomes modified with an angiopeptide-2 peptide, which allows the particles to traverse the BBB and target GBM cells.

Routes of Administration for Nano-Drug Delivery Systems

Intravenous Injection

Niu et al[142] successfully developed a novel biomimetic drug delivery system by immobilizing pH-sensitive adriamycin-containing heparin nanoparticles onto the surface of grapefruit-derived extracellular vesicles (GF-EVs). The system exhibited high delivery efficiency, prolonged circulation time, and glial-targeting ability. Blood-brain barrier crossing and glioma targeting were achieved via intravenous injection, resulting in excellent anti-glioma efficacy in vivo. Advantages of Intravenous Injection (IV) administration include no need for surgical or invasive manipulation and suitability for repeated dosing; Due to its inherent ease of operation, this method has been widely adopted as the primary drug delivery approach in most experiments involving targeted MMP nanocarrier systems. However, at the same time, there may be hazards of potential systemic toxicity.

Convection-Enhanced Delivery (CED)

This technique involves injecting therapeutic agents directly into tissues by applying positive pressure, thereby enhancing their diffusion into the target region.[143–145] Nanoparticles designed by Pang et al[146] were delivered to tumor tissues via

CED and cross the intact blood-brain barrier, thereby significantly enhancing their antitumor efficacy and ability to silence multiple genes associated with DNA repair promotion and cell invasion. This strategy offers a promising approach for the treatment of GBM. In addition, Wang et al[147] successfully circumvented temozolomide resistance by injecting platinum-based anticancer drug-loaded nanoparticles into glioblastoma xenograft mice using CED. This delivery method has the advantage of high targeting, but carries the risk of infection. Therefore, catheter design and material diffusion properties must be considered when implementing CED to ensure safety and efficacy.[143,148] The ability to cross the blood-brain barrier and enhance local drug concentration makes it widely used in glioma treatment and diagnosis. However, as no studies have yet explored the combined use of CED with MMP-targeted nanocarrier systems for therapy, further experimental research in this area is essential.

Focused Ultrasound (FUS) Combined with Microbubbles

A study was conducted using focused ultrasound (FUS) to transiently disrupt the Blood-Brain Tumor Barrier (BBTB) and deliver radiolabeled copper nanoclusters to diffuse gliomas. They hypothesized that once the drug is loaded onto the copper nanoclusters, the biodegradability of the copper nanoclusters could facilitate the rapid in situ release of the drug as it enters the tumor, making it a better treatment for diffuse tumor cells.[149] Advantages of combining microbubbles via FUS include the ability to precisely open the BBB and enhance delivery efficiency, but are device-dependent and may lead to CNS toxicity.[143,150] Previous studies have demonstrated that focused ultrasound delivery significantly enhances therapeutic efficacy of liposome-targeted MMP nanomedicine systems compared to conventional injection.[151]

The Combination of Nano-Drug Delivery Systems and MMPs

MMPs as Targets for Active Targeting

MMPs play a critical role in glioma progression and metastasis. Its concentration around the tumor will be higher than that in normal cells. Therefore, MMPs can be used as specific targets for designing targeted drugs, indirectly modulate gliomas by inhibiting MMPs.

Currently, most nano-delivery systems targeting MMPs are based on active recognition mechanisms. MMP-2 is one of the unique physiological properties of the glioma microenvironment that can selectively cleave multiple peptide sequences. These peptide sequences are also known as MMP-2 sensitive peptides. Common studies insert MMP-2-sensitive peptides between the inactivation sequences of cell-penetrating peptides, so that they do not exhibit permeability in general tissues. When they reach the site of gliomas, MMP specifically cleaves the MMP-sensitive peptides and simultaneously cleaves the inactivation sequences, allowing the cell-penetrating peptides to regain activity and enter tumor cells to release the drug. Hua et al[152] designed a glioma therapy nanocarrier called SynB3-PVGLIG-PTX, which integrates the MMP - 2 sensitive peptide PVGLIG with the membrane-permeable SynB3 and a specific therapeutic drug for glioma, paclitaxel (PTX) to realize target-accurate and efficient drug delivery. It can be specifically recognized and cleaved by MMP-2 after entering the BBB, releasing PTX to treat gliomas. Meanwhile, Gu et al[153] increased the cumulative concentration of PTX in gliomas by utilizing MMP-2-sensitive peptides to form an ALMWP-NP-PTX nanodelivery system. The above experiments showed that the concentration of drugs in gliomas can be increased more accurately by using MMPs as a targeting site, thus enhancing the anti-glioma effect of the drugs. Fan et al[154] utilized an MMP-2-activatable nanodrug delivery system to carry B7-H3 bispecific antibodies, thereby enhancing the induction of ferroptosis in glioma cells and treating gliomas.

MMPs as Therapeutic Targets

MMPs serve as important regulators of brain glioma development and metastasis. Its concentration is positively correlated with the degree of tumor invasion and is regulated by various metabolic pathways. Therefore, many studies have been undertaken to decrease concentrations of MMPs by modulating the metabolic pathway of MMPs or directly applying MMP inhibitors to treat gliomas. For example, Fan et al[155] designed a specific peptide, re-MM15, which down-regulated the phosphorylation level of FAK and the expression of MMP-2 protein in GBM xenograft tissues, which in turn may inhibit the metastasis and invasion of GBM. Meanwhile, Blázquez et al[156] found that cannabinoids selectively inhibited MMP-2 expression and reduced the degree of invasion of GBM in mice. Ni et al[71] found that a novel small

transmembrane glycoprotein SMAGP could inhibit the PI3K/AKT pathway in the MMP regulatory pathway to limit the expression of MMP-2 and -9, which in turn reduced the invasiveness of GBM.

There are few experimental studies on the modulation of MMPs by nanotechnology and MMPs are not used as the only therapeutic target. Li et al[157] designed Eu-Cs nanopolymers that can effectively control the release of the anti-glioma drug eugenol, which can significantly downregulate MMP-9 expression in GBM and reduce tumor metastasis. Meanwhile, limonene-loaded liposomes designed by Vinitha et al[158] effectively downregulated the expression of MMP-2, -9 in GBM and inhibited glioma angiogenesis. Using MMPs as therapeutic targets can effectively reduce the aggressiveness of gliomas and inhibit their angiogenesis, thus exerting an anti-glioma effect.

However, in early-generation experiments using MMP inhibitors to treat gliomas, these inhibitors alone did not exert a therapeutic effect on gliomas and required combination with chemotherapy to achieve therapeutic efficacy.[159] Moreover, in experiments where MMP inhibitors were used in combination with the chemotherapeutic drug temozolomide for glioma treatment, relatively severe toxic side effects—such as joint and tendon pain—were observed. This could be attributed to their poor selectivity.[160] Consequently, first-generation MMP inhibitors have never successfully passed clinical trials. However, with the further advancement of relevant technologies in recent years, numerous experiments have begun to design MMP inhibitors with higher selectivity, also known as second-generation MMP inhibitors. For instance, some studies have developed blood-brain barrier (BBB)-penetrating MMP inhibitors (MMPi) that not only specifically target MMP-2 and MMP-9 but also exhibit low cytotoxicity.[161] Nevertheless, more clinical trials are still required before they can be truly applied in the treatment of gliomas.

Advantages and Disadvantages of Nanomaterials in the Treatment of Gliomas

Nanotechnology is highly non-invasive in the treatment process. Since nanotechnology treatment for gliomas is non-invasive, it does not require open surgery or radiation therapy. Consequently, patients do not experience pain or other uncomfortable symptoms during the treatment.

Nanoparticles have great potential for precise targeting and drug delivery to cancer cells. The favorable physicochemical attributes of nanomaterials including nanoscale size, large surface-to-volume ratio, tunable architecture, inherent targeting propensity, and versatile surface chemistry enable them to function as precision drug carriers for tumor-targeted delivery. In addition, they are biologically safe and have a long circulation time in the bloodstream. Thus, they can prolong the circulation time of drugs and contrast agents in the brain, thereby reducing the dose and minimizing side effects.[162]

In addition, the nanomaterials can penetrate the BBB and be used as excellent transport carriers to deliver therapeutic medications straight to the site of brain tumors. However, this is difficult to achieve using traditional treatment methods.

In addition to the above advantages, there are a number of disadvantages and difficulties with using nanomaterials to treat gliomas. The primary issue lies in the inherent defects of these nanomaterials. For instance, certain polymer nanoparticles are prone to toxic degradation and the aggregation of toxic monomers. The major limitations of liposomes comprise their relatively short shelf life, limited embedding efficiency, inadequate stability, nonspecific cellular adsorption, and intermembrane transfer. A disadvantage of metallic nanomaterials is their toxicity. In addition, tumors also encounter many challenges and problems that need to be addressed in the process of targeting. Firstly, there is a dearth of suitable therapeutic targets. Despite the fact that dozens of drugs have progressed to clinical trials, well-defined and druggable targets remain scarce. Secondly, administering single-target drugs often results in the loss or downregulation of the original drug target. Drug resistance may emerge due to novel mutations in tumor cells. Third, numerous unresolved challenges persist in clinical translation and drug development.

The Role of CPPs in MMPs-Targeted Nano-Delivery Systems

Functions of CPPs

Cell-penetrating peptides (CPPs) are a class of small-molecule polypeptides comprising 5–30 amino acids. Their unique structure and charge properties enable them to penetrate the cell membrane barrier and efficiently carry themselves or biomolecules (eg drugs, nucleic acids, proteins, etc.) bound to them into the cell interior. These peptides can accomplish

transmembrane transport by interacting with lipids or receptors on the surface of the cell membrane, triggering mechanisms such as endocytosis or direct penetration.[163]

Due to its special functions, it is widely used in various medical fields. It can not only modify drug delivery carriers, but also improve the penetration of drug delivery systems, making it easier for them to reach the target location and play a role. At the same time, it not only can assist nucleic acid molecules and imaging agents to penetrate the cell membrane to complete transmembrane transport, but also plays an important role in gene editing and imaging. In recent years, with the continuous development of research, new cell membrane-penetrating peptides with more functions and better features have been developed. Thus, they have broad developmental prospects.

Application of CPPs in Nano-Drug Delivery Systems

Nano-drug delivery systems, as an emerging drug delivery technology in recent years, can utilize nanocarriers to carry drugs to the specific target sites in the body to exert their effects. In addition to drug-carrying nanocarriers, other modification components are needed to help the drug penetrate various barriers in the body, such as cell membranes and blood-brain barriers. Due to their ability to deliver drugs to the innermost layers of tissues, CPPs are widely used in many nano-delivery systems. For example, a study utilizing CPP containing the RI-AG03 peptide coupled to liposomes with polyR or TAT sequences promoted membrane penetration as well as macropinocytosis of the liposomes and increased the uptake of the carrier by the organism.[164] Meanwhile, a study that functionalized gold nanoparticles with CPP fragments via mercapto polyethylene glycol (PEG) to improve their stability and bioavailability resulted in a 46-fold increase in cellular uptake in A549 and B16 cell lines.[165] It has also been studied that a novel fusion peptide TAR composed of tumor-targeting peptide A7R and cell-penetrating peptide TAT was utilized to modify PTX, a potent breast cancer drug, to form nanoparticles. It remains stable in the normal environment, whereas it breaks and releases the drug in breast cancer. Precise management of breast cancer has been realized.[166]

Types of Activatable CPPs

Although CPPs play a key role in nano-delivery systems, their lack of selectivity, transport effects and poor stability are drawbacks that cannot be ignored. This can lead to the inability of the drug to reach the target location precisely despite its ability to penetrate deeper into the tissue. Therefore, modification using CPPs alone is not ideal. Targeting is generally required by adding specific targeting elements that inactivate CPPs in the general state and only become active again in a specific state. Such CPPs are referred to as activatable CPPs.[167]

Currently, the more common activatable CPPs are of the following types:

pH Activates CPPs

Various pH-sensitive CPPs have been designed to take advantage of the acidic microenvironment of tumors. Amit A Kale et al[168] prepared plasmids containing DNA (encoding the green fluorescent protein GFP) that had been further modified with TATp and PEG. PEG was attached to the liposome surface via pH-sensitive hydrazone bonds. The removal of the PEG coating due to the reduced intra tumor pH resulted in the exposure of liposome-attached TATp residues. Thus, tumor cells can be efficiently transfected, enhancing the permeability of liposomes within the tumor cells and enabling more effective intracellular gene delivery. Vivian Juang et al[169] reported liposomal and solid lipid nanoparticles (SLN) consisting of CPP, ligands targeting the tumor neovascular system that undergoes angiogenesis, and mitochondria-targeting peptides. In colon cancer HCT116 cells, the nanoparticles exhibited pH-responsive release, internalization, and intracellular dispersion at acidic pH. According to the experimental findings, pH-responsive targeted nanoparticles might offer a viable way to treat colorectal cancer.

The Enzyme Activates CPPs

Since MMPs degrade tumor stroma and promote tumor metastasis, various MMP-activatable CPPs have been designed using this function. Wu et al[170] developed an amphiphilic invisible peptide coating consisting of an amphiphilic antifouling sequence, an MMP-9 cleavable sequence, and a cell-penetrating Tat sequence. The photothermal gold nanorods (AuNRs) were protected by this coating. The experimental results indicated that MMP-9-sensitive

multifunctional peptide-coated AuNRs are promising nanomaterials. It can increase the accumulation of tumor tissue and extend somatic circulation, resulting in a more targeted and efficient tumor treatment. In addition, a novel set of personalized nanocarriers has been proposed. By integrating enzyme-activatable CPP sequences with mesoporous silica-coated quantum dot nanoparticles, this approach enables real-time monitoring of intracellular drug transport and regulated anti-tumor medication administration that targets the nucleus.[171]

Endosomal Escapable CPPs

After internalization, the extracellular material is encapsulated in vesicular compartments called endosomes. This is another obstacle that limits the effectiveness of drug delivery. To address this issue, Xu et al[172] developed a CPP covalently modified quantum dot composed of TAT and the endosomal peptide HA2. The quantum dots were delivered into mammalian cells with high efficiency as well as minimal cytotoxicity, thus enhancing their internalization in mammalian cells.

The Synergistic Effect of CPPs and MMPs

Among the above activatable CPPs, the most widely used in tumor therapy is MMP-modified enzyme-activatable CPPs. MMP, as a tumor-specific enzyme, has been utilized by a number of scholars to synergize MMP with CPPs to complement nano-delivery systems for the precise delivery of tumor drugs. One study, for instance, used dual-functionalized MMP substrates by utilizing the cell-penetrating peptide PepFect14 (PF14), allowing it to be dual-functionalized with PEG and substrates. This allowed CPPs to be specifically expressed in tumors while avoiding normal tissues.[173] Meanwhile, some studies have inserted matrix metalloproteinase-2 cutting sites between the CPPs and inactivation sequences. So that when it reaches the tumor site, its high concentration of MMPs will cut the inactivation sequence, thus activating the CPPs to play a penetrating role.[174]

It can be seen that CPPs and MMPs co-modified nanosystems have a great potential for tumor drug therapy. However, the balanced relationship between selectivity and penetration needs to be investigated further.

Prospects or Questions Raised

The nanoparticle drug delivery system, leveraging its unique nanoscale properties, including small size and surface effects, is expected to realize the precise drug delivery to the glioma site through targeting MMPs and crossing the BBB. This prospect indicates that the treatment of gliomas will progress to a new stage of emerging and more efficient treatment. However, this therapeutic mechanism is accompanied by challenges: (1) how to precisely regulate the MMP recognition sites on the surface of the nanoparticles to avoid non-specific binding; (2) how to ensure that the nanoparticles remain structurally stable and effectively release the drug in the complex brain tumor microenvironment, while reducing their potential toxicity to normal brain tissue.

We propose a novel therapeutic strategy in which the synergistic action of CPPs and MMPs enables nano-drug delivery systems to efficiently cross the BBB and precisely target the release of drugs for glioma treatment. This is an innovative strategy that combines targeted drug delivery and tumor microenvironment regulation. The application of this technology is promising: (1) CPPs can help drugs break through the blood-brain barrier by promoting transmembrane transport, thereby enhancing drug penetration. (2) As MMP expression is elevated in the malignant glioma region, MMPs-responsive vectors can be precisely targeted to reduce damage to normal tissues.

In addition, this technology can face many challenges: (1) Although CPPs can enhance drug penetration, the integrity of the BBB in glioma patients varies depending on tumor grade and location, with high-grade gliomas showing more significant barrier disruption, which may weaken the specificity of targeted delivery. (2) Resistance issues in the tumor microenvironment. (3) Safety issues: The nonspecific transmembrane ability of CPPs may lead to drug accumulation in healthy brain tissues, resulting in potential toxic effects.

Conclusion

We comprehensively analyze the expression patterns and regulatory mechanisms of MMPs in gliomas, emphasizing their crucial roles in tumor microenvironment remodeling, angiogenesis, and metastatic progression. Furthermore, we explore

the transformative potential of nano-drug delivery systems in glioma therapy. These systems enable targeted drug delivery, controlled release kinetics, and enhanced bioavailability, offering innovative strategies to overcome therapeutic challenges in gliomas.

Focusing on CPPs, we summarize their applications in nano-drug delivery systems, with particular emphasis on activatable CPPs. We introduce a novel approach integrating MMP-modified, enzyme-activatable CPPs, which synergize with MMPs as targeted and therapeutic targets in combination with nano-drug delivery systems.

In conclusion, this review not only provides novel perspectives on glioma therapy but also offers actionable insights for future research. By elucidating MMP mechanisms in gliomas and utilizing innovative nano-drug delivery systems applications, we anticipate significant improvements in treatment efficacy and patient prognosis.

Data Sharing Statement

The data analyzed in this review are derived from publicly available studies published in peer-reviewed journals, as cited in the reference list. Specific quantitative results can be found in the original articles, which are accessible through databases like PubMed and Web of Science using the provided citations. No new data were generated for this review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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