Current standing and frontiers of gene therapy for meningiomas

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Meningiomas are among the most common intracranial tumors. The treatment of choice for these lesions is complete resection, but in 50% of cases it is not achieved due to tumor location and/or surgical morbidities. Moreover, benign meningiomas have high recurrence rates of up to 32% in long-term follow-up. Molecular analyses have begun to uncover the genetics behind meningiomas, giving rise to potential genetics-based treatments, including gene therapy. The authors performed a literature review on the most relevant genes associated with meningiomas and both current and potential gene therapy strategies to treat these tumors. Wild-type *NF2* gene insertion, oncolytic viruses, and transfer of silencing RNA have all shown promising results both in vitro and in mice. These strategies have decreased meningioma cell growth, proliferation, and angiogenesis. However, no clinical trial has been done to date. Future research and trials in gene insertion, selective inhibition of oncogenes, and the use of oncolytic viruses, among other potential treatment approaches, may shape the future of meningioma management. (<http://thejns.org/doi/abs/10.3171/2013.8.FOCUS13305>)

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MENINGIOMAS are typically slow-growing tumors of the central nervous system (CNS) that originate from arachnoid cap cells, which belong to the outermost layer of the arachnoid mater. Meningiomas are the second most common primary adult neoplasm of the CNS after glioblastoma multiforme (GBM), with an annual estimated incidence of 2.3 cases per 100,000 persons.^{71,72} Most of these tumors are considered benign, but although 5-year survival rates reach 90%, 20-year survival rates are approximately 53%.⁸⁰ Intracranial meningiomas represent 98% of all CNS meningiomas (spinal lesions denote approximately 2% of cases).³¹ Several risk factors have been associated with the development of these tumors, among them female sex, hormone-replacement therapy, advanced age, deletions of the *neurofibromin 2* (*NF2*) gene, ionizing radiation, and head trauma.^{8,16,26,36} Meningiomas are more commonly sporadic, yet they can be hereditary in patients with neurofibromatosis Type 2, multiple endocrine neoplasia Type 1, or Li-Fraumeni, Turcot, Gardener, von Hippel-Lindau, Cowden, or Gorlin syndrome.³⁸

Abbreviations used in this paper: Ad = adenovirus; GBM = glioblastoma multiforme; GWAS = genome-wide association study; HSV = herpes simplex virus; siRNA = small interfering RNA.

The current standard of care for patients with meningiomas is gross-total resection of the tumor,³⁷ a feat that is sometimes difficult to achieve due its location and/or surgical morbidities. Hence, complete resection is achieved in less than 50% of patients,²⁷ and recurrence rates in macroscopically complete tumor removal (Simpson Grades 1–3) are up to 32% after 15 years of follow-up.⁸⁰ On the other hand, radiation-based treatments and chemotherapy have potential benefits for patients with these neoplasms, but the role of these therapeutic approaches in the management of meningiomas is limited to cases of subtotal resection or when tumors are virtually inaccessible due to their critical location.^{12,47,66}

Over the last years, there has been an increasing attention to the molecular genetics of meningiomas. Research has been focused on tumor-suppressor genes, oncogenes, and cell-signaling pathways, including their role on the development, aggressiveness, and recurrence of these tumors.^{3,16,51,65,75} The resulting information has led the way for an increasing interest in potential genetics-based treatments. These novel procedures, particularly gene therapy, aim to treat meningiomas by genetically modifying the cancerous cells.⁷⁶ Neurosurgeons must recognize the importance of knowing the principles behind genetics-based treatments and their potential therapeutic benefits, in as

much as the future of medicine will tend toward less invasive, more selective and safer treatment options.

In this article, we first present a concise review of the genes currently known to be associated with the etiology and pathophysiology of intracranial meningiomas. We then describe the principles behind genetics-based treatments for neoplastic disorders, and finally focus on the current standing and frontiers of these treatments applied to meningiomas.

Histopathology and Genetics of Meningiomas

The World Health Organization (WHO) categorizes meningiomas into several grades based on cell type, mitotic activity, cellularity, necrosis, and brain invasion. The benign type (WHO Grade I) is the most common, representing 80% of all cases. This type is followed by atypical (WHO Grade II, 15%–20%) and anaplastic (WHO Grade III, 1%–3%) meningiomas.⁷¹ Grade I tumors are histologically classified as meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, or metaplastic. Grade II meningiomas are more aggressive and are classified as clear cell or choroidal. Grade III meningiomas are considered malignant and are divided into rhabdoid or papillary subtypes.⁵³ Unfortunately, the specific molecular genetic basis for such diverse histological subtypes has not been yet determined.⁶⁵

Tumor suppressor genes encode proteins that regulate and suppress cell proliferation by inhibiting progression of the cell throughout the cell cycle. Inactivation of tumor suppressor genes and consequently uncontrolled cell proliferation occurs when both alleles become nonfunctional, according to Knudson's two-hit hypothesis.⁴⁸ The *NF2*⁸³ and *CDKN2A*⁹ genes are examples of tumor suppressor genes involved in meningiomas. Proto-oncogenes on the other hand encode proteins involved in regulation and promotion of cell growth and proliferation. These genes may suffer a change in their genetic sequence or a loss of regulation, thus creating oncogenes. Oncogenes will now uncontrollably promote cell proliferation and potentially cause neoplasia; *c-sis* (*PDGFB*)⁵⁶ and *c-myc*²⁰ (*MYC*) are examples of oncogenes involved in meningiomas.

Recently, a prostaglandin D synthase (PGDS)-positive meningeal cell has been identified as a possible precursor cell to meningiomas. Researchers found that the inactivation of *NF2* in embryonic PGDS-positive cells was related to the heterogeneity of meningioma histological subtypes.⁴³

Genes Involved in Meningioma Tumorigenesis

The main tumor suppressor gene involved in early meningioma tumorigenesis is *NF2* (Table 1).^{16,65} Alterations in the *NF2* gene are the most common cytogenetic abnormalities found in meningiomas;¹⁶ most neurofibromatosis Type 2 meningiomas and up to 78% of sporadic meningiomas have deletions in chromosome 22q.⁶⁸ This gene is found on chromosome 22q and encodes for a protein called merlin, whose main function is to link the cell membrane proteins to the cytoskeleton. Recent studies have revealed that merlin also plays a role as part of the actin cytoskeleton and is involved in the regulation of cell

proliferation and growth and the initiation of neoplastic behavior.^{30,77}

The *DAL-1* gene has a debated role in meningioma tumorigenesis; it encodes for the 4.1B protein, which belongs to the same superfamily as merlin. 4.1B acts as a regulator of cell proliferation and apoptosis and has also been associated with tumor initiation, but to a much lesser extent than *NF2*.⁶³

The main oncogenes involved in meningioma tumorigenesis are *Ha-ras* and *c-mos*.⁶⁵ Their role in initiation of neoplastic behavior is yet much less understood than that of *NF2*.^{21,68}

Genes Involved in Meningioma Cell Growth

The major genes involved in cell growth are oncogenes *c-fos* (*FOS*), *c-myc* (*MYC*), and *c-sis* (*PDGFB*) (Table 2).^{65,68} *C-fos* and *c-myc* are nuclear transcription-regulating genes; both are overexpressed in meningiomas, with research indicating a probable involvement in growth factor autocrine loop signaling.^{20,40} *C-sis* is also overexpressed in meningiomas; it encodes a component of platelet-derived growth factor- β , suggesting a role in cell growth and maintenance.^{44,56}

Genes Involved in Higher Meningioma Grade

The most important tumor suppressor genes associated with higher meningioma grade are *TIMP1*, *TIMP3*, *CDKN2A*, *CDKN2B*, *CDKN2A* (*p14[ARF]*), and *NDRG2* (Table 3).¹⁶ Tissue inhibitors of matrix metalloproteinases (TIMPs) have the task of regulating matrix metalloproteinase (MMP) activity, cellular proliferation and angiogenesis.²⁸ Inactivation or lower activity of both *TIMP1* and *TIMP3*, mainly through methylation, has been associated with a more invasive and higher-grade meningioma idiosyncrasy.^{6,35} Chromosome 9 harbors the genes *CDKN2A*, *CDKN2B*, and *CDKN2A* (*p14ARF*). All three are regulators of cell cycle progression at the G1/S phase checkpoint.⁶⁵ Complete losses of 9p or more subtle homozygous deletions of these genes have been found in higher-grade meningiomas.⁹ Lastly, *NDRG family member 2* (*NDRG2*, also known as *N-Myc downstream-regulated gene 2*) has been found to be downregulated in anaplastic and atypical meningiomas with aggressive behavior.⁵⁴

The major oncogenes associated with higher meningioma grade are *Bcl-2* (*BCL2*), *STAT3*, and *TP73*.⁶⁵ All of these genes have been found to have higher expression rates in higher-grade meningiomas.^{1,88}

Cell Signaling Pathways

Cell signaling pathways control various processes such as cell differentiation and proliferation. The Hedgehog and Wnt signaling pathways have been associated in the progression of meningiomas,⁶⁵ and to a lesser extent the Notch, transforming growth factor- β , and insulin receptor signaling pathways have also been associated with these tumors.^{17,42,64,84}

The Principles Behind Genetics-Based Treatments for Cancer

Gene therapy involves the artificial allocation of ge-

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TABLE 1: Major genes involved in meningioma tumorigenesis*

Gene	Type	Locus	Encoded Protein	Function
<i>NF2</i>	TSG	22q12.2	merlin	cell membrane linkage to cytoskeleton; cell growth and proliferation
<i>DAL-1 (EPB41L3)</i>	TSG	18p11.32	4.1B protein	cell membrane linkage to cytoskeleton; regulator of apoptosis & cell proliferation
<i>Ha-ras (HRAS)</i>	oncogene	11p15.5	p21	cyclin-dependent kinase inhibitor
<i>c-mos (MOS)</i>	oncogene	8q11	c-mos protein	serine kinase

* TSG = tumor suppressor gene.

netic material (complete genes or gene segments) into a host cell. General somatic gene therapy strategies include gene augmentation therapy, targeted killing of specific cells, and targeted inhibition of gene expression.⁷⁶ Gene augmentation therapy is useful for diseases caused by loss of function of a gene. Direct cell killing is possible when inserted genes cause cellular apoptosis (suicide genes) or when the expressed gene increases susceptibility of the cell to be killed by a specific drug. Targeted mutation correction involves correction of resident mutations when they produce a dominant-negative effect, and lastly targeted inhibition of gene expression allows for selective blocking of single genes at the DNA, RNA, or protein level.⁷⁶

Gene therapy aimed at treating neoplastic disorders also involves general approaches including artificial killing of cancer cells, stimulation of natural killing of cancer cells, use of oncolytic viruses (explained in *Gene Therapy for Brain Tumors*), and protecting the surrounding normal tissues from effects of chemotherapy/radiotherapy (Fig. 1).⁷⁶

Patients with tumors arising from inactivation of tumor suppressor genes can benefit from gene augmentation therapy or from insertion of wild-type tumor suppressor genes. Patients with tumors resulting from oncogene activation may benefit from selective inhibition of gene expression, delivery of gene-specific ribozymes to cleave oncogene mRNA, or the use of intracellular antibodies to specifically bind to and inactivate the oncoprotein.

Technology of Gene Therapy

Gene transfer can occur outside or inside the patient's body. Ex vivo therapy involves the removal of target cells from a patient, growth in culture, genetic modification, and finally reimplantation of these cells into the host. This therapy is useful when target cells are accessible for removal and have long survival times after replacement. Such is the case for hematopoietic and skin cells.⁷⁶ In vivo therapy involves the transfer of genetic material to target cells within the patient. This becomes the only option when target cells cannot be cultured in vitro in adequate

numbers (as with brain cells) or when treated cells cannot be reimplanted effectively.

Once a specific strategy for the treatment of cancer has been chosen, the challenge now becomes how to deliver the genetic material to the cancer cell. Size of the DNA fragments is sometimes limited by the vector capacity, but this limitation can be circumvented by transferring small artificial minigenes.⁷⁶ After the genes have been transferred to the host cell, the genetic material may integrate into the chromosome of the cell or remain as an extrachromosomal gene (episome). Integration of the gene into the chromosome has the advantage of perpetual and long-term expression through cell division. Nonetheless, insertion occurs randomly and therefore the gene may not be expressed at all or may even cause cell death.⁷⁶ On the other hand, episomes may have a more stable expression rate, but long-term expression now becomes an issue because when cells divide; the newly introduced gene may segregate unequally to daughter cells.

The specific delivery system used in gene therapy depends on the target tissue, the size of the genetic material, and whether therapy is in vivo or ex vivo. Transfer of genetic material via viral vectors is called transduction, and this is the most commonly used method of delivery,⁸¹ because viral vectors are very effective in infecting cells, transferring genetic material, and inducing construct expression. The use of nonviral vectors is called transfection, and it usually involves naked DNA plasmids, lipoplexes (spherical vesicles composed of synthetic lipid bilayers), or other inorganic nanoparticles.⁸² Viral vectors have the advantage of having higher transduction efficiency and longer-term gene expression, but they are associated with immunogenicity, carcinogenicity, poor target cell specificity, gene size transfer limitation, and high costs.¹⁰ Nonviral methods offer the ability to transfer larger genes and easy and safe preparation with no immunogenicity. Nonetheless, nonviral methods have lower efficiency and target gene expression than viral methods.^{19,50}

Targeting of viruses or other vehicles to specific tissues also poses a challenge.²⁴ Targeting can be done at the

TABLE 2: Major genes involved in meningioma cell growth

Gene	Type	Locus	Encoded Protein	Function
<i>c-fos (FOS)</i>	oncogene	14q24.3	c-fos protein	transcription factor; autocrine loop signaling
<i>c-myc (MYC)</i>	oncogene	8q24	c-myc protein	transcription factor; autocrine loop signaling
<i>c-sis (PDGFB)</i>	oncogene	22q13.1	β -chain of PDGF- β	growth factor

TABLE 3: Major genes involved in higher-grade meningiomas

Gene	Type	Locus	Encoded Protein	Function
<i>TIMP1</i>	TSG	Xp11.3-p11.23	metalloproteinase inhibitor 1	inhibits MMP-9; regulation of cellular proliferation & apoptosis; angiogenesis
<i>TIMP3</i>	TSG	22q13.1	metalloproteinase inhibitor 3	inhibits MMP-9 & MMP-2; regulation of cellular proliferation & apoptosis; angiogenesis
<i>CDKN2A</i>	TSG	9p21.3	p16 protein	cell cycle control
<i>CDKN2B</i>	TSG	9p21.3	p15 protein	cell cycle control
<i>CDKN2A (p14[ARF])*</i>	TSG	9p21.3	p14arf protein	cell cycle control
<i>NDRG2</i>	TSG	14q11.2	NDRG2 protein	growth & apoptosis regulator
<i>BCL2</i>	oncogene	18q21.33	bcl-2 protein	apoptosis regulator
<i>STAT3</i>	oncogene	17q21.2	signal transducer & activator of transcript 3	transcription factor
<i>TP73</i>	oncogene	1p36.3	p73	apoptosis factor

* Product of an alternate reading frame of *CDKN2A*.

level of virus cell binding and entry or after virus uptake. Entry targeting can be achieved through modifications of the outer virus membrane, thus granting the virus the ability of selective binding. Redirection of viruses to alternate cell surface molecules can also be attained by using specific adapter molecules and by insertion of ligands.^{34,62} Postentry targeting takes the form of transcriptional targeting, where mutations of specific viral genes create strains that are inefficient for replication in normal cells but efficient in cancerous cells.²⁴

Gene Therapy for Brain Tumors

The use of gene therapy for brain tumors has been mostly focused on treatments for GBM utilizing viral vectors.^{2,4,18,41,61} Therapeutic viruses exist in the form of genetically engineered replication-competent or replication-incompetent viruses. The former function as oncolytic viruses, and the latter function solely as vectors.¹⁸ Oncolytic viruses selectively infect cancer cells, replicate within them, and cause cell lysis.¹⁵ Viruses currently investigated for use in brain cancer include herpes simplex viruses (HSVs), adenovirus (Ad), vaccinia virus, retrovirus, and others.

HSV-1 is a double-stranded DNA virus with a genome of approximately 80 genes (152 kb). Genetic alterations in

the *thymidine kinase* gene (*TK*),⁵⁵ ribonucleotide reductase *ICP6/RR* and/or *ICP34.5/γ34.5*, for example, restrict viral replication to rapidly dividing cells^{11,59,85} and create safer oncolytic viruses.^{45,70} This modification prevents viral replication in normal brain tissue, preventing life-threatening encephalitis. Deletion of essential immediate early genes (for example, *ICP4* and *ICP27*) can render a replication-defective HSV-1, which can be used solely as a vehicle for delivery of therapeutic genetic material.⁶⁰

Adenoviruses are also double-stranded linear DNA viruses but with a smaller genome (36 kb) compared with HSV.¹⁸ These viruses can be turned replication-incompetent by deletions in early regions of their genomes (E1A, E1B, E2, E3, or E4) or through substitution of essential genes with a specific therapeutic gene of interest.⁷ Adenoviruses can be used to deliver tumor suppressor genes to cancerous cells (wild-type insertion of tumor suppressor gene) or prodrug activation enzymes such as the HSV-thymidine kinase. Delivery of wild-type *p53* to brain tumor cells has been tested, with evidence showing inhibition of glioma growth both in vitro and in vivo.^{49,58} Oncolytic adenoviruses are also emerging as an alternative therapy for patients with brain tumors.⁴¹

Vaccinia virus is an enveloped double-stranded DNA virus with a life cycle of less than 6 hours.¹⁸ This virus can

Fig. 1. General strategies of gene therapy for neoplastic disorders.

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be used as an effective vector after targeted deletion of its vaccinia growth factor (*VGF*) and *TK* genes.⁵⁷ Delivery of *p53*, *IL-2*, and *IL-12* in a combined synergistic treatment has shown inhibition of glioma growth in mice.¹⁴

Retroviruses are unique since they use reverse transcriptase to convert their genetic information into DNA before being integrated into the host genome. Retrovirus vectors have been mainly used to deliver suicide genes to cancer cells, which have shown to increase cell vulnerability to chemotherapeutic agents and induce cell apoptosis.¹⁸ HSV-*TK* has been delivered to tumor cells via retroviruses, increasing cell sensitivity to ganciclovir.⁷⁸

Other viruses that can also be used in gene therapy are the Newcastle disease virus, reoviruses, vesicular stomatitis virus, poliovirus, and the measles virus. Additionally, not all viral vectors are created equal.⁸¹ For instance, adenoviruses are able to transduce nondividing and dividing cells and carry up to 8 Kbp of heterologous DNA, but they are highly immunogenic. HSV is well suited as an oncolytic virus and can carry up to 50 Kbp of heterologous DNA, but it poses the risk of residual cytotoxicity and most humans have partial immunity against it.

Another gene therapy strategy that can be applied is using stem cells as oncolytic virus carriers.⁶¹ An advantage to this method is that viruses can be dispensed intravascularly, thus evading antiviral immunity and being able to reach the tumor from a distance. Mesenchymal stromal cells loaded with Ad-Δ24RGD have been able to migrate to and infect intracerebral gliomas, whereas Ad-Δ24RGD alone was unable to do so.⁸⁷

Current Standing of Genetics-Based Treatments for Intracranial Meningiomas

Meningiomas are the second most common primary intracranial tumor, comprising approximately 30% of CNS primary neoplasms.²⁷ For over 100 years the treatment of choice has been complete resection, but unfortunately this cannot always be achieved. Recurrence rates of meningiomas are high, and we are just beginning to understand the molecular genetics that drive these tumors.

Compared with GBM, little work has been done on clarifying the genetic basis for meningiomas. Only a few gene expression studies, including one genome-wide association study, have been performed to date.^{23,29,84} A literature review of the most relevant studies revealed numerous attempts of gene therapy for meningiomas in the last 17 years (Table 4). Gene therapy strategies that have been employed include wild-type gene insertion, oncolytic virus use, using plasmids to transfer small interfering RNA (siRNA) to meningiomas, and other strategies. Although some studies have shown promising results, virtually none have been applied to clinical trials.

In 1998, Chauvet et al. used a replication-defective adenovirus bearing the *Escherichia coli* β-galactosidase gene (*LacZ*) to selectively transduce a primary canine meningioma.¹³ The adenovirus was rendered replication-defective by replacing the early viral regions E1A and E1B with the *LacZ* gene. A 14-year-old, 8-kg female West Highland Terrier with an olfactory groove meningioma was selected as a candidate for viral injection. The recom-

binant virus was injected directly into tumor vessels, and 5 days later, tumor tissue was assessed for viral gene delivery with X-Gal staining. No viral-related cytotoxicity was found, and the study demonstrated that meningiomas could be efficaciously transduced with adenovirus vectors.

In 1999, Ikeda et al. tested the viability of gene therapy by transferring a wild-type *NF2* gene into both *NF2*-positive and *NF2*-negative human meningioma cells in vitro.³⁹ The study compared HSV, adenovirus, and retrovirus vectors, and found that HSV-mediated *NF2* gene transfer lead to overexpression of the *NF2* product in target cells, which lead to a statistically significant inhibition of meningioma cell proliferation.

Shu et al. constructed a recombinant adenovirus with a mutant *Ha-rasNI7* gene, which is a Ras pathway inhibitor.⁷⁴ Meningioma cells were infected with this virus in vitro, and cell proliferation was measured labeling and detection assays. Suppression of Ras proteins in meningioma cells inhibited proliferation of all exponentially growing cells.

Dirven et al. investigated whether adenoviruses could continue to be effectively used for gene transfer to meningioma cells in vitro.²² A recombinant adenovirus expressing the *luciferase* gene was found to bind to meningioma cells expressing Coxsackievirus and adenovirus receptor (CAR), endothelial growth factor receptor (EGFR), and alpha integrins (ITGAVs). Targeting of adenoviruses to EGFR and ITGAVs was accomplished through the use of bispecific single-chain antibodies and an RGD (arginine-glycine-aspartic acid) sequence, respectively. *Luciferase* gene transfer was increased 3- and 9-fold when the adenovirus was targeted to EGFR and ITGAVs, respectively.

The use of oncolytic viruses for meningioma treatment has also been investigated. Grill et al. modified an adenovirus to replicate selectively in retinoblastoma-mutant cells, showing significant oncolytic activity in benign, atypical, and malignant meningiomas in vitro.³² The adenovirus strain that was used was generated through replacement of the gp-19k open reading frame in E3 with the *luciferase* gene. Yazaki et al. engineered an HSV that inhibited cell growth considerably in higher-grade meningiomas in mice.⁸⁶ This strain of HSV, termed G207, had deletions at both γ34.5 loci, which are required for replication in brain tissue and encephalitis pathogenesis; the *LacZ* gene was also added.

Tummalapalli et al. used plasmid vectors to transfect siRNA constructs for cathepsin B and MMP-9 both in vitro and in vivo.⁷⁹ Compared with controls, meningioma cells treated with bicistronic siRNA plasmids showed decreased migration and invasion.

In 2011, Gupta et al. also used plasmid vectors to transfect siRNA constructs for uPAR/cathepsin B and uPA/uPAR; the authors studied the effect of the constructs on meningioma cells, using them alone as well as in combination with radiation.³³ Small interfering RNA (siRNA), also known as “silencing RNA,” interferes with gene expression, particularly with complementary nucleotide sequences. In this study, siRNA was able to interfere with both uPAR/cathepsin B and uPA/uPAR, which are proteolytic pathways of the urokinase-type plasminogen activator system. These systems have been found to be in-

TABLE 4: Literature review of accomplishments in gene therapy for intracranial meningiomas

Authors & Year	Gene Therapy Strategy	Vector	Study Type	Result
Yazaki et al., 1995	oncolytic viruses	HSV	in vivo (mice)	inhibition of meningioma cell growth
Chauvet et al., 1998	wild-type <i>LacZ</i> gene insertion	Ad	in vivo (dog)	effective <i>LacZ</i> transduction
Ikeda et al., 1999	wild-type <i>NF2</i> gene insertion	HSV, Ad, retrovirus	in vitro	inhibition of meningioma cell proliferation
Shu et al., 1999	wild-type <i>Ha-rasN17</i> gene insertion	Ad	in vitro	inhibition of meningioma cell proliferation
Dirven et al., 2002	wild-type <i>luciferase</i> gene insertion	Ad	in vitro	effective <i>luciferase</i> gene transfer
Grill et al., 2005	oncolytic viruses	Ad	in vitro	inhibition of meningioma cell proliferation
Tummalapalli et al., 2007	siRNA transfer	plasmid	in vitro/in vivo (mice)	decreased migration & invasion of meningioma cells
Gupta et al., 2011	siRNA transfer	plasmid	in vitro/in vivo (mice)	decreased angiogenesis in meningioma

involved in meningioma tumorigenesis, via increasing the expression of angiogenic molecules such as Ang-1, Ang-2 and VEGF. Both constructs were able to reduce angiogenesis compared with controls, both in vitro and in vivo.

Frontiers

Gene therapy is a potential treatment option for meningiomas that is still in development. Even though replication-defective and oncolytic viruses have been investigated as potential vectors in gene therapy for meningiomas, and the *NF2* gene has already been transferred to meningioma cells in vitro, there have not been any clinical trials to date. Other potential gene therapy strategies (Fig. 2), such as insertion of the *MDR1* gene or selective inhibition of oncogenes, have not been fully explored.

The most important limitation in gene therapy for meningiomas is that the molecular and genetic basis of tumorigenesis, progression, and malignancy is not yet fully understood. Although molecular analyses have begun to uncover the roles that tumor suppressor genes, oncogenes, and signaling pathways play in the biology of meningiomas, more research is needed in the form of large-scale genome-wide association studies and high-throughput sequencing.⁶⁵ At the same time, safe and effective gene transfer methods must also be research topics. Two clinical

trials on gene therapy for GBM failed due to a very poor rate of gene delivery to tumor cells.^{67,69}

It must not be forgotten that cancer is a very complex disease and is oftentimes the result of multiple mutations and genetic aberrations. Gene transfer into each individual cancer cell is virtually impossible, so research should also be focused on the transfer of genes encoding therapeutic proteins (including apoptosis-inducing proteins,⁷³ immunostimulatory factors,^{25,52} and prodrug-activating enzymes⁴⁶) that attack tumors as a whole and not only individual cells. Gene therapy must not be idealized as a single-therapy alternative but visualized as part of a strategic combination that has the ultimate goal of working synergistically to best treat a patient.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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FIG. 2. Current and potential gene therapy strategies for meningiomas.

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