

Review Article

Spinal cord astrocytomas: progresses in experimental and clinical investigations for developing recovery neurobiology-based novel therapies

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ABSTRACT

Spinal cord astrocytomas (SCAs) have discernibly unique signatures in regards to epidemiology, clinical oncological features, genetic markers, pathophysiology, and research and therapeutic challenges. Overall, there are presently very limited clinical management options for high grade SCAs despite progresses made in validating key molecular markers and standardizing tumor classification. The endeavors were aimed to improve diagnosis, therapy design and prognosis assessment, as well as to define more effective oncolytic targets. Efficacious treatment for high grade SCAs still remains an unmet medical demand. This review is therefore focused on research state updates that have been made upon analyzing clinical characteristics, diagnostic classification, genetic and molecular features, tumor initiation cell biology, and current management options for SCAs. Particular emphasis was given to basic and translational research endeavors targeting SCAs, including establishment of experimental models, exploration of unique profiles of SCA stem cell-like tumor survival cells, characterization of special requirements for effective therapeutic delivery into the spinal cord, and development of donor stem cell-based gene-directed enzyme prodrug therapy. We concluded that precise understanding of molecular oncology, tumor survival mechanisms (e.g., drug resistance, metastasis, and cancer stem cells/tumor survival cells), and principles of Recovery Neurobiology can help to create clinically meaningful experimental models of SCAs. Establishment of such systems will expedite the discovery of efficacious therapies that not only kill tumor cells but simultaneously preserve and improve residual neural function.

1. Introduction

Gliomas are tumors that arise from glial cells. They make up about 30% of all brain and spinal cord (i.e., the central nervous system: CNS) tumors. Intramedullary spinal cord tumors (IMSCTs: tumors within the parenchyma) are the rarest of primary spinal cord tumors with high grade ones causing severe neurologic deterioration, functional deficit or death. IMSCTs comprise 8 to 10% of all primary spinal cord tumors, which in turn account for 2 to 4% of all CNS tumors (Chamberlain and Tredway, 2011; Minehan et al., 2009) (Fig. 1). This is in contrast to intracranial gliomas, which comprise ~80% of all malignant tumors in the brain. Spinal cord gliomas can be sub-classified based on their cellular origin, with 60 to 70% classified as ependymomas and 30 to 40% classified as astrocytomas, followed by hemangioblastomas and other rare lesions (Babu et al., 2014; Milano et al., 2010).

Astrocytomas are a group of cancers derived from presently defined tumorigenic astrocytes of the CNS. Based on the most commonly used grading system established by the World Health Organization (WHO), astrocytomas are graded from I (least advanced disease with best prognosis) to IV (most advanced disease with worst prognosis). High grade SCAs fortunately are rare relative to other types of CNS cancers in humans. However, to date they remain to be the most difficult entities for clinical management due to their tenacious growth/metastasis, poor response to chemoradiotherapy, and difficulties or outcome uncertainty for surgical interventions (Abd-El-Barr et al., 2016). Although there are many similarities between astrocytomas of the spinal cord and those of the brain, there are important differences. These differences account for both the variations in tumor cell behaviors and importantly, in the tactics of devising research strategies to develop targeted therapies. For these reasons the review is mainly focused on high grade SCAs, with

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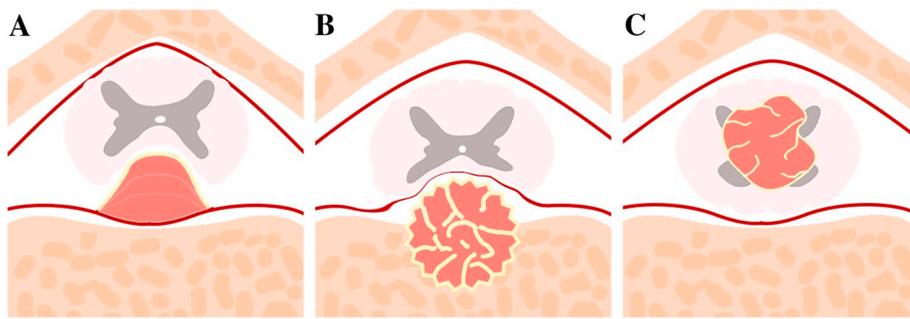


Fig. 1. The three general pathological types of spinal tumors.

(A) Extradural neoplasms: The majority of neoplastic lesions (~ 60%) grow extradurally and originate from the vertebrae, for which metastasis is the most frequent cause. (B) Extramedullary neoplasms: Intradural tumors are relatively rare with the extramedullary tumors being the more common type (~30%). Lastly, (C) intramedullary neoplasms: Intramedullary tumors are the least common (~10%) among all spinal tumors. However, they occur most often in the cervical levels of the spinal cord and comprise predominantly gliomas (i.e., in-

filtrative astrocytomas and ependymomas), imposing tenacious resistance to conventional treatments.

highlights shed on molecular oncologic genetics, research advances, and the different therapies that are currently used or under development for the management of SCAs.

2. Epidemiology

To judiciously design translational research approaches to treating high grade SCAs, it is important for laboratory investigators to first grasp the specific epidemiology feature of this group of tumors. Primary spinal cord gliomas occur in a very low incidence rate of 0.22 per 100,000 person-years (Milano et al., 2010; Schellinger et al., 2008). In regards to age preference, ependymomas are more common in adult spinal cord, while astrocytomas comprise 90% of IMSCTs in pediatric patients (Karsy et al., 2015; Ostrom et al., 2014b), showing a possible inclination of astrocytoma cells to grow in the biochemical and signaling regulation environment of the developing spinal cord. For SCAs, a recent examination of the Surveillance, Epidemiology and End Results (SEER) database revealed that most patients presented their first clinical signs during the first 3 decades of life and most had low grade lesions (Grades I or II) at time of diagnosis (Milano et al., 2010). Ependymomas, by contrast, were more likely to present between the ages of 40 and 59, with a majority being Grade I. A large retrospective review of all primary SCAs seen at the Mayo Clinic over 40 years uncovered an average age of 35 years at disease presentation, with 60% of patients being male (Minehan et al., 2009). The clinical manifestation of spinal cord gliomas is determined in large part by the location and growth profile of the tumor (Fig. 1). However, pain appears to be the predominant symptom in the majority of cases (~70%), which can be presented as back pain, radicular pain, or central pain (Raco et al., 2005). The next most common presentation is sensory deficit (~65%), followed by motor deficit (~50%). The duration of symptoms before diagnosis is usually protracted due to the nonspecific nature of the symptoms, with one large series uncovering an average symptom duration of 3 years (Raco et al., 2005). The occurring sites of these tumors are nearly evenly divided amongst cervical, thoracic and lumbar segments (Abdel-Wahab et al., 2006; Raco et al., 2005).

For WHO's conventional grading of astrocytomas, Grade I describes juvenile pilocytic astrocytoma or cystic cerebellar astrocytoma (and its variant juvenile pilomyxoid astrocytoma) that occurs more often in children and young adults (i.e., in the first 20 years of life). Astrocytoma Grade II (also called Low-Grade Astrocytoma) are diffuse tumor types such as fibrillary, gemistocytic, protoplasmic astrocytoma that tend to invade surrounding tissue and grow at a relatively slow pace. Grade III consists of anaplastic astrocytomas that are malignant and grow more aggressively. They often trigger seizures, neurologic deficits, headaches, or changes in mental status. Lastly, Grade IV comprises glioblastoma multiforme (GBM) that is the most malignant with poorest prognosis (Louis et al., 2007; Parsa et al., 2005; Zadnik et al., 2013). In its most current iteration, the WHO has incorporated molecular parameters in addition to histological grading in its classification schema (Louis et al., 2016). Noticeably, IMSCTs only account for 2% to 10% of all CNS tumors and for ~15% of primary intradural

spinal tumors in adults (Heo et al., 2012; Sturm et al., 2012; Yang et al., 2012). Among them, about 70% are tumors of low malignant potential, such as low-grade astrocytomas and ependymomas (Schwartzentruber et al., 2012). However, a report on primary spinal cord tumors diagnosed between 1998 and 2002 showed that about 31% were Grade III or IV malignant tumors and 69% were Grades I or II non-malignant tumors (Schellinger et al., 2008).

2.1. Molecular biology and genetics of SCAs

Since standard treatment of SCAs involves maximal safe resection, followed by chemoradiation and there has been conflicting evidence for surgery efficacies, the reality has made tissue availability much scarcer for enabling systematically designed genetic and genomic studies to be carried out. For what have been published, the role of isocitrate dehydrogenase 1 (*IDH1*) and *IDH2* genes has become important in the understanding of tumorigenesis and prognosis of SCAs, which were used effectively for generating the 2016 WHO classification of astrocytomas (Sturm et al., 2012; Zadnik et al., 2013). The mutations lead to abnormal DNA methylation as they cause an abnormal production of 2-hydroxyglutarate that normally inhibits histone demethylases (Yang et al., 2012). The rate of *IDH1* mutations in SCAs is presently not clear despite frequent detections of *IDH1* mutations in autopsy samples of SCAs (Heo et al., 2012).

An important gene regulating methylation is the histone 3 variant H3.3 (H3F3A), which has been implicated in the tumorigenesis of both intracranial and spinal cord astrocytomas (Schwartzentruber et al., 2012; Wu et al., 2012). Two mutations, Lys27Met and Gly34Arg in H3F3A have been identified in nearly 80% of glioblastomas (i.e., Grade IV astrocytoma) in the brainstem, an anatomical structure that connects the spinal cord with the brain (Schwartzentruber et al., 2012; Wu et al., 2012). The Lys27 residue was found to be abnormally methylated in *IDH1* mutant glioblastoma – underlying the importance of epigenetic modification in CNS tumorigenesis (Sturm et al., 2012; Yang et al., 2012; Zadnik et al., 2013). The mutation of H3F3A K27M is predominantly detected in malignant astrocytomas arising in structures of the midline of the body, including the thalamus, brain stem, and spinal cord and was listed as a separate entity in the 2016 WHO classification (Louis et al., 2016; Solomon et al., 2016). Worth noting is the suggestion that the K27M mutation may be a marker of primary astrocytoma in the spinal cord and hence an indicator of the worst prognosis probability (Nagaishi et al., 2016).

Also on the list of important tumor markers is the BRAF gene (Schindler et al., 2011; von Deimling et al., 2011). BRAF is a member of the mitogen-activated protein kinase (MAPK) pathway which is important for cell survival including cellular division, cell cycle progression and excessive growth (i.e., malignant transformation; Penman et al., 2015). It has been shown that in a majority of pilocytic astrocytomas, a previously uncharacterized gene, KIAA1549, and the BRAF gene form a fusion oncogene that causes constitutive BRAF kinase activation (Jones et al., 2008). Detailed mutational analysis of the BRAF gene determined a valine to glutamate substitution at position 600

(BRAF V600E), resulting in constant activation of the MAPK pathway (Davies et al., 2002). The combination of the V600E mutation and a homozygous deletion of CDKN2A, which encodes P14ARF and P16INK4A, in human neural progenitor cells have been demonstrated to induce tumor cell transformation that manifested morphologic and pathologic features most close to those of malignant astrocytomas (Huillard et al., 2012). These mutations thus carry important prognostic and therapeutic impact, with fusion-negative patients showing better length of survival (LOS) and progression-free survival (PFS) compared to fusion-positive patients (Horbinski et al., 2012; Penman et al., 2015). In fact, numerous studies have uncovered that supratentorial pilocytic astrocytomas are more likely to harbor the BRAF V600E mutation, while posterior fossa and spinal cord pilocytic astrocytomas are more likely to harbor fusion oncogenes (Horbinski et al., 2012). A multi-institutional study of SCAs found that 80% of Grade I astrocytomas harbored mutations in the BRAF genes, among which 40% harboring the BRAF-KIAA1549 translocation and the other 60% having a BRAF copy number gain (Shankar et al., 2016). Interestingly, none of their specimens harbored the BRAF V600E mutation. The same study also found a preponderance of the K27M mutation in their series of Grade III and IV SCAs, suggesting that occurrences of the BRAF and H3F3A may segregate based on the grading of the astrocytoma, which should be additionally examined to establish possible prognostic utilities (Shankar et al., 2016).

Based on the profiles of the clinical manifestations and molecular causal factors of SCAs we hypothesized that these marker genes are primarily involved in regulating cell survival endeavors; when functioning in pathological scales they drive intractable growth of high grade SCAs. Our postulation is supported by outcomes of a systematic analysis of representative oncogenes of spinal cord astrocytoma (Table 1) that shows that most of the genes (i.e., in orange and red color zones) that have been established for clinical diagnosis and progression utility are indeed in charge of cell survival, not conventionally defined stemness biology (Teng et al., 2018). This conclusion suggests that cancer cell survival mechanisms, in addition to stemness events that may be related to cancer occurrence, should be targeted for developing clinically meaningful therapeutics (Teng et al., 2018). As the field moves forward from histopathological grading of both intracranial and spinal cord gliomas into molecular grading, the efficacy of accurate experimental tumor modeling, and clinical tumor diagnosis, prognosis assessment and therapeutic plan design for SCAs will continuously be improved. The advancement has been additionally strengthened by validation of regulatory roles of microRNA (miR: small non-coding ribonucleic acid molecules that function primarily in RNA silencing and/or post-transcriptional regulation of gene expression) in cancer diagnosis and prognosis. This approach has been widely used in basic science settings and especially for evaluating clinical prognosis of SCAs (Table 2), further enriching the repertoire and sophistication of clinical diagnosis, prognosis assessment, academic reasoning, and research tactics to tackle SCAs.

Additionally benefited from this technology advancement is clinical efficiency since less tissue is needed for performing molecular diagnoses versus conventional histopathologic assays (Shankar et al., 2016). As a result, all the previously known problems concerning spinal cord tissue inadequacy and possibility of worsening neurological function due to biopsy procedures are and will be further mitigated.

2.2. Current therapeutic approaches for SCAs

Surgical treatment: There is currently no consensus on the best treatment for infiltrating SCAs. Oftentimes, there is a real need of tissue biopsy for diagnostic purpose as radiology imaging itself cannot differentiate between the different types of IMSCTs or other pathologies such as transverse myelitis, demyelination, infection, or even spinal cord infarction. For both intracranial and spinal cord astrocytoma cases, there is evidence that the extent of the surgical resection positively

influences the patient LOS and PFS (Garces-Ambrossi et al., 2009; Karikari et al., 2015; McGirt et al., 2008). However, this correlation is tempered by surgery-triggered onset of neurological worsening that has been associated with poorer clinical outcomes (McGirt et al., 2009; Rahman et al., 2017). The latter has been considered as a very serious challenge regarding treatment plan formation for this category of tumors, which was caused by the conventional goal of cancer treatment (i.e., to remove tumor mass as much as possible). Unlike intracranial astrocytomas, the extreme functional eloquence of the spinal cord and its associated axonal tracts make the surgery utterly difficult, if not impossible to achieve a gross total resection (GTR) of SCA without causing additional permanent neurological deficits to the patient. Accumulated data suggested that histological grading, which affects infiltrative nature of the astrocytoma appears to be the most important factor to predict whether or not a dissection plane between the tumor and the spinal cord can be found and hence whether or not a GTR can be achieved (Toktas et al., 2018; Abd-El-Barr et al., 2016; Karikari et al., 2011). Indeed, for low-grade gliomas, especially grade I pilocytic astrocytomas, often a dissection plane could be determined for carrying out a GTR without subjecting the patient to a neurological deficit. In these cases, aggressive surgical approaches under intraoperative magnetic resonance imaging assistance are normally advised in order to give the patient the best chance of increased survival and lower the risk of recurrence (Toktas et al., 2018). By contrast, for Grade III or IV SCAs, such a dissection plane simply does not exist; thus, aggressive surgical resection is not recommended as this will subject the patient to more neurological deteriorations with some of them frequently being permanent. For those cases, surgical options are truly limited and qualitatively improved prognosis relies on targeted cancer therapy that has been under development (Ropper et al., 2016; Zeng et al., 2016). Typically, a biopsy with expansile duraplasty is used as the safest option to establish a definitive diagnosis and the space created may temporally alleviate clinical signs caused by continued growth of the tumor. Even for biopsy intraoperative neuromonitoring is strongly advised to assist the surgeons to mitigate possibilities of causing complications and to strive to remove as little tissue as is needed to enable a diagnosis (Verla et al., 2016). Similar to advances being made in intracranial mapping techniques, newer intraoperative neuromonitoring techniques are designated to helping to identify safer passages to these intramedullary tumors for surgical approaches without triggering neurological deficits (Deletis and Sala, 2008; Nair et al., 2014). Although presently surgery intervention is not recommended for treating patients with high grade and infiltrating SCAs, rapid intraoperative diagnosis of molecular markers and histopathologic profiles via glioma biopsy is a promising direction of development in the immediate future as we are learning more about the oncological features of these different subtypes of malignant tumors for designing targeted therapies (see details below; Shankar et al., 2015).

Radiation therapy and chemotherapy: The role of radiotherapy for managing SCAs remains debatable and controversial. Although adjuvant or postsurgical radiotherapy has been adopted worldwide, the exact effects on SCAs have not been systematically examined and validated. Conceivably, for low grade SCAs, only limited benefits can be speculated for post-operative radiotherapy due to the spontaneous low recurrent rates of the tumors that argue against any real necessity for the patients to have radiation exposure for its known side effects (Epstein et al., 1992; Rodrigues et al., 2000). Rather, radiotherapy is indicated postoperatively for cases of partial resection and high grade SCAs (Jyothirmayi et al., 1997). Nevertheless, some research data suggested that a slight advantage of overall survival may be attainable for radiotherapy of low grade astrocytomas via enhanced control of tumor growth (Jyothirmayi et al., 1997; Santi et al., 2003). This effect may be true particularly for patients under 25 years old (Guss et al., 2013). Conversely, the risk of secondary malignancy and growth retardation that have been indicated in pediatric patients radiotherapy should be factored in except, perhaps in very special circumstances such as cancer recurrence (Kutluk et al., 2015).

Table 1
Common molecular markers used to diagnose spinal cord astrocytomas (SCAs)

Gene	Full Name	Wide Type Protein	Function	Mutation Protein	Oncological Features
<i>IDH</i>	Isocitrate Dehydrogenase	IDH1 (Cytoplasm)	NADPH production; Defense against oxidative stress (Jo et al., 2001)	IDH1 R132H (R132S, R132C, R132G, and R132L)	D-2-hydroxyglutarate (D-2HG) accumulation in tumor cells, which contributes to tumorigenesis, cell growth and survival (Zhao et al., 2009); Remodeling the methylome of DNA and establishing glioma-specific G-CIMP (Turcan et al., 2012).
		IDH2 (Mitochondria)		IDH2 R172K	
<i>H3F3A</i>	H3 histone family member 3A	H 3.3 (Nucleus)	Nucleosome structure of the chromatin. It supports chromosomal heterochromatic structures, which maintains genome integrity during mammalian development (Jang et al., 2015).	Lys27Met	Cancer cell migration (Park et al., 2016) and DNA hypomethylation (Bender et al., 2013); Alternatively lengthening of telomeres; Affecting specific gene expressions (Schwartzentruber et al., 2012) and tumorigenesis (Bjerke et al., 2013).
				Gly34Arg	
				K27M G34R/G34V	
<i>TP53</i>	Tumor protein p53	p53 (Nucleus and/or cytoplasm)	Initiating apoptosis, activating DNA repair, arresting growth by cell cycle regulation, and inhibiting angiogenesis, cellular renew and differentiation (Ryan et al., 2001).	Deletion	Tumor development and radioresistance (Squarrito et al., 2010).
<i>CDKN2A</i>	Cyclin Dependent Kinase Inhibitor 2A	p16INK4a and p14ARF (Nucleus)	Cell cycle regulation (Ichimura et al., 2000), inhibition of cell proliferation and telomerase activity (Fuxe et al., 2000).	Point Mutation Deletion	Cell proliferation (Mistry et al., 2015) Resistance of antimetabolite agents (Iwadata et al., 2000)
<i>CDKN2B</i>	Cyclin Dependent Kinase Inhibitor 2B	p15INK4b (Nucleus)	Regulating cell growth and the cell cycle G1-S progression (Wrensch et al., 2009b). It has been recognized as an effective “backup” for loss of CDKN2A (Krimpenfort et al., 2007).	Point mutation Deletion	Tumorigenesis and cell proliferation (Simon et al., 1999). Its variants are associated with high-grade glioma susceptibility (Wrensch et al., 2009a).
<i>PTEN</i>	Phosphatase and tensin homolog	PTEN (Cytoplasm)	Inhibitor of PI3K/AKT signaling pathway: maintaining genomic stability, and suppressing cell survival and cell proliferation (Yin and Shen, 2008).	Point Mutation Deletion	Activation of PI3K/AKT pathway, angiogenesis, tumorigenesis (Cheney et al., 1998; Smith et al., 2001).
<i>NF1</i>	Neurofibromin 1	Neurofibromin (Cytoplasm)	GTPase-activating protein and negative regulation of RAS/MAPK pathway activity (Johannessen et al., 2005)	Mutation (R1391S, R1513*, e25-1, e29 +1, etc.) Heterozygous deletions	Inactivation of neurofibromin, activation of RAS/MAPK pathway, and suppression of apoptosis (Johannessen et al., 2005; Tanic et al., 2012).
<i>BRAF</i>	B-Raf Proto-Oncogene, Serine/Threonine Kinase	BRAF (Cytoplasm)	Regulation of the MAP kinase/ERK signaling pathway, which controls cell cycle entry, proliferation, and integration of mitogen and stress signals for proliferation (Yang et al., 2017).	BRAF V600E (R461I, I462S, G463E, G463V, G465A, G465E, etc.) K1A01549-BRAF	Activate MAPK/ERK signaling pathway; Promote cell proliferation and transformation, or formation of anchorage independent colonies (Liu et al., 2007).
<i>EGFR</i>	Epidermal growth factor receptor	EGFR (Cell membrane)	Cellular proliferation, growth, differentiation, and survival (Oda et al., 2005; Reddy et al., 2016).	vIII mutants	Constitutive activation of EGFR and its downstream proliferative and antiapoptotic pathway. Cell proliferation and invasion (Micallef et al., 2009). Radioresistance and DNA repair (Lammering et al., 2003).

(continued on next page)

Table 1 (continued)

Note: Color coding: Green zone genes and molecules mainly regulate cell metabolism and proliferation, or repair DNA damages (i.e., tumor suppressors); their mutations can trigger SCA occurrence. Orange zone genes and molecules largely promote cell proliferation and cell survival under physiological condition. Red zone genes are those with mutations such as genetic deletion, which turns on their ability to promote cell survival by augmenting cell proliferation, migration and drug-tolerance, as well as by suppressing apoptosis (Bender et al., 2013; Bjerke et al., 2013; Cheney et al., 1998; Fuxe et al., 2000; Ichimura et al., 2000; Iwadate et al., 2000; Jang et al., 2015; Jo et al., 2001; Johannessen et al., 2005; Krimpenfort et al., 2007; Lammering et al., 2003; Liu et al., 2007; Micallef et al., 2009; Mistry et al., 2015; Oda et al., 2005; Park et al., 2016; Reddy et al., 2016; Ryan et al., 2001; Simon et al., 1999; Smith et al., 2001; Squatrito et al., 2010; Tanic et al., 2012; Turcan et al., 2012; Wrench et al., 2009a; Wrench et al., 2009b; Yang et al., 2017; Yin and Shen, 2008; Zhao et al., 2009).

For high grade SCAs that generally have low sensitivity to radiation treatment, a recent systematic review of overall survival in a pediatric series showed that adjuvant radiotherapy improved general outcome of primary spinal glioblastoma multiforme (Konar et al., 2017), which is different from results from previous studies (Fakhreddine et al., 2013; Santi et al., 2003). Given the lack of large multicenter studies, it

appears that prospective clinical trials are needed to further clarify the role of radiotherapy, with a focus on differing results in different pathological types, molecular grade of SCAs, and patient profiles (e.g., age, gender, clinical history, etc.).

Currently, established chemotherapy regimens are also considered to have limited value in the treatment of SCAs. It is commonly reserved

Table 2
micro RNAs (miRs) currently used as prognostic indicators for spinal cord astrocytomas (SCAs)

MicroRNAs	Full Name	Function	Clinical Value
miR-126	MicroRNA-126	Likely having effect on suppressing angiogenesis (Han et al., 2016)	Potential marker for postsurgical prognosis evaluation for patients with brain glioblastoma (Han et al., 2016)
miR-106a	MicroRNA-106a	Suppress cell proliferation and induce apoptosis (Zhang et al., 2012)	Independent and significant predictor of prognosis in glioblastoma patients (Zhao et al., 2013)
miR-130a	MicroRNA-130a	Suppress angiogenesis (Chen et al., 2008), and promote cancer migration, invasion and proliferation (Jiang et al., 2015)	Marker of favorable prognosis (Qiu et al., 2013)
miR-181d	MicroRNA-181d	MiR-181d directly regulates MGMT post-transcriptionally (Zhang et al., 2012)	Biomarker to predict temozolomide response (Zhang et al., 2012)
miR-326	MicroRNA-326	Regulate cell survival (Kefas et al., 2010)	Marker of favorable prognosis; An important candidate as a tumor suppressor (Wang et al., 2013)
hTERT mRNA	Telomerase messenger ribonucleic acid	Maintenance of telomeric DNA at the ends of chromosomes (Kang et al., 2016)	A potential prognostic factor and diagnosis marker (Shervington et al., 2007; Löttsch et al., 2013)
MiR-21	MicroRNA-21	Suppress cell apoptosis (Chan et al., 2005)	Poor prognostic marker (Hemansen et al., 2013)
miR-155	MicroRNA-155	Regulate cell invasion and chemosensitivity (Liu et al., 2015)	Poor prognostic marker (Qiu et al., 2013)
miR-182	MicroRNA-182	Facilitate cell migration and promote cell survival (Segura et al., 2009)	Prognostic marker for glioma progression and patient survival (Jiang et al., 2010)
miR-210	MicroRNA-210	Promote a hypoxic phenotype and radioresistance (Grosso et al., 2013)	Poor prognostic marker (Qiu et al., 2013)
miR-215	MicroRNA-215	Promote tumor growth by activating the CTNBP1/ β -catenin pathway (Tong et al., 2015)	Poor prognostic marker (Tong et al., 2015)
miR-637	MicroRNA-637	Promote cell growth, migration and invasion via direct targeting Akt1 (Que et al., 2015)	Poor prognostic marker (Que et al., 2015)

Note: Green color-coded miRs are associated with more favorable prognosis; red color-coded miRs and mRNA are associated with poor outcomes of SCAs (Chan et al., 2005; Chen and Gorski, 2008; Grosso et al., 2013; Han et al., 2016; Hermansen et al., 2013; Jiang et al., 2010; Jiang et al., 2015; Kang et al., 2016; Kefas et al., 2010; Liu et al., 2015; Löttsch et al., 2013; Qiu et al., 2013; Que et al., 2015; Segura et al., 2009; Shervington et al., 2007; Tong et al., 2015; Wang et al., 2013; Zhang et al., 2012; Zhao et al., 2013).

for patients with tumor recurrences after surgery and radiotherapy. Temozolomide, an oral methylating agent, has become standard therapy in newly diagnosed adult intracranial GBM (Hegi et al., 2005; Stupp et al., 2005). There are, however, small study series that have shown encouraging results for low-grade SCAs, with 18% of patients having a partial response and no major adverse reactions (Chamberlain, 2008). For high-grade astrocytomas, small retrospective series have shown some benefits, with ~40% of patients showing a partial response, albeit more hematological side effects were noted (Kaley et al., 2012; Kim et al., 2011). In addition, antiangiogenic treatments have also shown certain effects. Bevacizumab is such an antiangiogenic agent that targets vascular endothelial growth factor (VEGF). Small size retrospective studies have suggested a palliative impact for the use of bevacizumab in spinal cord gliomas that manifested persistent progression despite surgical resection, radiation therapy and temozolomide therapy (Chamberlain and Johnston, 2011).

Kaley et al. reported that administration of temozolomide and bevacizumab may be beneficial in the recurrence of spinal cord high-grade gliomas after radiotherapy (Kaley et al., 2012). A pilot study assessing the long term outcome of combinatorial chemoradiation treatments suggested that the approach was feasible and could serve as a therapeutic option (Corradini et al., 2016). But due to the small size of the patient population, different origins of tumors and limitations of retrospective investigations, convincing evidence remains lacking to standardize chemoradiation for SCAs (Corradini et al., 2016).

2.3. Experimental investigation and therapy development

Based on the afore-described data, it is clear that SCAs are extremely difficult oncologic entities to treat. This is partly attributable to the inherently aggressive biology of these tumors, but also due to the eloquent structures of the spinal cord, making aggressive surgical treatment – an important intervention, not applicable in SCAs, especially for infiltrating neoplastic lesions. Thereby, basic science investigations and experimental therapies should become the focal point in order to eventually overcome SCAs. However, most experimental endeavors have to date been carried out for the research and treatment development of intracranial gliomas, leaving IMSCTs as an understudied topic. Consequently, there are very few experimental models being established for investigating SCAs in vivo. In the next section, we reviewed some of the promising investigations, comprising establishing clinically relevant models, stem-cell therapies, gene therapies and immunotherapies, all aiming to devising targeted treatments, with emphasis on how to effectively eliminate the diffusely infiltrating astrocytoma cells and preserve the residual neural network in the spinal cord, particularly for the segments that sustain vital functions (e.g., cervical spinal cord for respiratory and circulation functions).

2.4. Experimental models of IMSCTs

The migratory and diffuse growth feature of high grade astrocytoma cells in the spinal cord and brain often renders surgical treatment *per se* insufficient and not feasible. A powerful approach to changing this situation is to first set up experimental models of IMSCTs with high clinical face value. Prior to our work that was published in 2016, there had been only 3 articles describing how to design rat models of intramedullary spinal cord gliomas. All three protocols reported reproducible intramedullary growth of glioma by directly injecting 9L gliosarcoma, 98L glioma, or glioblastoma multiforme neurosphere cells into the middle or lower thoracic spinal cord level (Caplan et al., 2006; Hsu et al., 2012; Ren et al., 2010). The lower thoracic spinal cord tumors produced hindlimb locomotion deficits, which were used for testing standard behavioral batteries to define the survival duration of the affected rats.

However, in humans the cervical and cervicothoracic junction regions of the spinal cord with enriched autonomic neural components

are more common sites for the multitude of growth of intramedullary astrocytomas. Thus, autonomic disorders are often presented by the patients, which, sometimes, have life-threatening consequences (Furlan et al., 2003; Krassioukov et al., 2009; Osborn et al., 1990; Teasell et al., 2000). More research effort is therefore needed to establish cervical spinal cord models of high grade SCAs. We recently designed a rat C6 model of SCAs by implanting G55 or U87 human astrocytoma cells, and characterized the pathophysiological profile by assessing positive correlations between the scale of C6 tumor growth with degrees of abnormality in the somatomotor and sensory systems, respiratory function, blood pressure, heart rate, body temperature, and body weight (Ropper et al., 2016). Furthermore, we investigated whether human NSCs (hNSCs; see below for details) could be genetically engineered into effector cells to carry out gene-directed enzyme prodrug therapy (GDEPT) for controlling midcervical SCAs, tapping into hNSC's chemotactic capability to track cancer cells following the chemical concentration gradients of the ligands (e.g., VEGF, CXCL-12, etc.) produced by the tumor and/or inflammatory cells (Ropper et al., 2016; Teng et al., 2011; Schmidt et al., 2005). In our model, the non-treated control C6 SCA rats showed significantly decreased respiratory rate and correspondingly increased inspiration time phase during the late stage of tumor growth. The data of respiratory change was consistent with clinical observation in patients with cervical SCAs-related bilateral diaphragm weakness who often show the so-called “poor inspiratory effort” because about 70% of tidal volume in humans is normally attributable to the inspiratory work of the diaphragm, in contrast to rodent's breathing activity that is driven more by the force derived from the intercostal and abdominal muscles (McCool, 2012; Teng et al., 1999). C6 SCA model also exhibited progressive disturbance of blood pressure and body temperature. For example, beginning at the third week after G55 astrocytoma cell transplantation, rats without receiving effective treatment showed significantly decreased group average systolic arterial blood pressure (SP). Their group mean arterial blood pressure (MAP = DP + 1/3 x [SP – DP]; DP: diastolic blood pressure) reduced significantly at the terminal stage when they could not consistently perform body weight-bearing locomotion (Ropper et al., 2016). The MAP data suggested that the cervical tumor growth might have compromised systemic tissue blood perfusion in the C6 SCA rats (Teng and Wrathall, 1996). This notion was corroborated by changes of body temperature in the same set of rats; we observed more severe hypothermia in the C6 SCA rats starting in the third week after tumor cell injection (Ropper et al., 2016). Academically, the C6 SCA model was also investigated in an innovative way to understand adult mammalian spinal cord neurobiology through characterizing its functional adaptation in response to the gradually escalated assaults and damages of infiltrating tumor cell growth to the axonal tracts and neurons. We hope that the approaches will ignite more research investment to research and therapeutic development for SCAs and other currently intractable metastatic diseases (Ropper et al., 2016).

2.5. Stem Cell-based gene directed enzyme prodrug therapy (GDEPT)

Neural stem cells (NSCs) are multipotent cells that are capable of generating gliogenic or neurogenic progeny (Teng et al., 2017; Llorens-Bobadilla and Martin-Villalba, 2017). There are generally four main sources for mammalian (including primate) NSCs to be isolated or derived for basic research and translational study applications: the neurogenesis niches of the subgranular zone (SGZ) of the young or adult hippocampal dentate gyrus, the subventricular zone (SVZ) of the lateral ventricles or the hypothalamus in developmental and adult brains, the embryonic stem cells (ESCs), and the inducible pluripotent stem cells (iPSCs) (Aboody et al., 2011). One of the functional multipotency features of NSCs is that these cells possess an exquisite tumor-tropism property that is enabled by their developmental capability of chemotactic migration (Aboody et al., 2000; Kim et al., 2005; Teng et al., 2011, 2012, 2017). Thereby, NSCs are able not only to track down and

move close to clusters or individual astrocytoma cells *in vitro* they can also track and infiltrate tumor masses *in vivo* (Aboody et al., 2000; Schmidt et al., 2005; Kim et al., 2005; Ropper et al., 2016). These properties of NSCs make them powerful vehicles to locally deliver anti-cancer genes and drugs with minimized systemic side effects. Buoyed by this innate biology of stem cells, many genetic engineering strategies have been formulated to equip NSCs with molecular mechanisms such as synthesis of a particular enzyme (i.e., GDEPT) that can convert a specific non-toxic prodrug into an oncolytic compound (Aboody et al., 2000; Ropper et al., 2016; Zeng et al., 2016). Hence, after the NSCs have migrated into the cancer cell's vicinity, a benign prodrug can be systemically administered for killing cancer cells via the afore-described “bystander effect” (Aboody et al., 2000; Ropper et al., 2016; Zeng et al., 2016).

Following completion of many well-designed animal studies, there was a recently published report on a phase-I clinical study that evaluated safety of applying an immortalized human NSC system in brain glioma cases (Portnow et al., 2017). Briefly, 15 patients with recurrent brain glioblastomas were treated with a one-time intracranial administration of the genetically engineered NSCs that expressed cytosine deaminase (HB1.F3.CD.C21) that converts the prodrug 5-fluorocytosine (5-FC) to the cytotoxic 5-fluorouracil (5-FU). Investigators found no evidence of dose limiting toxicity (DLT) due to the injected CD-NSCs. However, there was one case of DLT (i.e., transaminitis) occurrence, which was considered to be likely caused by 5-FC (Portnow et al., 2017). Microdialysis evaluation revealed that the cytotoxic drug 5-FU was produced in the brain in a 5-FC dose-dependent manner and autopsy results from 2 patients deceased from disease progression revealed that the donor NSCs migrated to infiltrate distant tumor sites without donor-related tumorigenic signs. Although the primary end point in this study was safety and the sample size was very small, efficacy could be loosely inferred by the fact that those patients receiving higher doses of the NSCs were found to have a longer median overall survival compared to those patients that received lower doses. However, based on our observation of the significantly diminished functional deficits in C6 SCA rats that received hNSC-based GDEPT and the functional multipotency of NSCs (e.g., production of trophic factors, etc.), it is important to examine whether the administered hNSCs also enhanced residual brain tissue preservation and function by activating alternative neural circuits (Ropper et al., 2016, 2017; Teng et al., 2011, 2017) or even through the potential of forming new neurons to integrate into the neurocircuit (Teng et al., 2017). Encouragingly, the same technology has been successfully used to engineer human mesenchymal stromal stem cells (hMSCs) to investigate and treat brain glioblastoma (Chung et al., 2016). However, more work is needed to reveal molecular specifics for the widely recognized pro- and anti-oncogenic properties of hMSCs in order to judiciously apply them for tumor control purposes (Chulpanova et al., 2018). We reiterate that integration of such Recovery Neurobiology principle (i.e., augmenting residual neural tissue sparing and function, or activating alternative neural pathways; Ropper et al., 2017) into the conventional oncolytic approach that solely focuses on killing tumor cells may synergistically increase the overall efficacy of cancer therapy.

In our premiere study, a clonal hNSC line (i.e., F3.hNSC) was engineered to express either cytosine deaminase gene only (i.e., F3.CD) or dual genes of CD and thymidine kinase (i.e., F3.CD-TK) to carry out GDEPT in a rat model of midcervical SCA (Ropper et al., 2016). F3.CD or F3.CD-TK cells were injected into the tumor epicenter 7 days after C6 tumor seeding. The C6 SCA rats that received the treatment of the F3.CD-TK NSCs plus systemic administration of 5-FC and Ganciclovir (GCV), prodrug of 5-FU and GCV triphosphate that are converted by CD and TK, respectively, lived significantly longer than those received F3.CD only or F3.hNSC debris followed with the same formula of 5-FC and GCV treatment (Ropper et al., 2016). Since the U.S. Food and Drug Administration lately approved the first clinical study evaluating a CD-engineered hNSC therapy for recurrent high-grade glioblastomas in the

brain (Portnow et al., 2017), we are currently investigating more oncolytic strategies in newly established experimental models following the Recovery Neurobiology principles, aiming to ultimately translate our findings for treating patients suffering from high grade astrocytoma (Karikari et al., 2011; Snyder and Teng, 2012; Ropper et al., 2016, 2017).

2.6. Direct gene therapy and gene editing

Traditionally, gene therapy has been defined by the addition of new genes to human cells. Nevertheless, a new paradigm has emerged with the advent of genome-editing techniques, where the human genome can be retailed to achieve a therapeutic effect (Friedmann and Roblin, 1972; Maeder and Gersbach, 2016; Maguire et al., 2014). The major catalyst behind the genome-editing techniques was the discovery that targeted DNA double stranded breaks (DSBs) could be used to “hijack” the cell's endogenous cellular repair mechanisms to delete deleterious genes or re-express lost genes that are therapeutically needed (Takata et al., 1998). Maeder and Gersbach reviewed the four primary methods of causing targeted DSBs – Zinc finger nucleases, transcription activator-like effector (TALE)-nucleases (TALENs), meganucleases, and the most recent CRISPR/Cas system (Maeder and Gersbach, 2016). Description of the specifics of these different methods is beyond the scope of this paper. It is worth noting that the CRISPR/Cas mechanism is derived from a system that was evolved in bacteria; it is a prokaryotic immune system that provides defense to foreign genetic molecules such as those present within plasmids and phages. The fact clearly indicates that even in the 21st century the knowledge and capability of humans to biotechnologically simulate nature's basic ways of maintaining genetic homeostasis still remain in a very early stage of development (Barrangou et al., 2007; Horvath and Barrangou, 2010; Wiedenheft et al., 2012).

Logically, as these technologies begin to capture attention in the science and clinical communities, their safety-related questions and potential ethic issues are also arising. Among them, how to control and reach the designed specificity of the genome-editing or gene delivery in using these genome-editing tools is one of the top concerns (Maeder and Gersbach, 2016). For now data obtained from intracranial glioblastoma studies suggested that a convergence of methods, rather than exclusive methods may be a better approach to overcoming the adaptive mechanisms used by glioblastomas to evade a conventionally standardized treatment (O'Duibhir et al., 2017).

2.7. Targeted immunotherapy

The role of the immune system in cancer tumorigenesis has long been recognized, from the empirical observation that immunosuppressive regimens or immunosuppressive states are accompanied with an increase in the incidence of malignancy (Calinescu et al., 2015; Doll and Kinlen, 1970). Conversely, both solid and hematologic cancers have been shown to progress more slowly or even gradually disappear when a targeted immune response is elicited (Burnet, 1967; Calinescu et al., 2015; Ostrom et al., 2014a). From these observations, the concept of immune surveillance was born, where it was hypothesized that the immune system is responsible for the continuous monitoring and elimination of cells harboring neoplastic mutations. Reciprocally, it has been observed that cancer cells are capable of producing immunosuppressive cytokines, which could lead to their escape from immune surveillance. With its regards to the CNS, there has long been a dogma that the CNS is immunoprivileged (Fecci et al., 2014). This was first suggested based on experiments in the 1940s in which skin grafts transplanted into the brain of experimental animals avoided rejection (Medawar, 1948). However, subsequent studies have modified this dogma: instead of absolute immunologic privilege, a concept that CNS has its distinct immunological processes was formed (Dunn et al., 2012).

Due to the demand in medical practice, most of the preclinical and clinical efforts on developing immunotherapy for CNS gliomas have so far targeted Grade-IV astrocytomas. In general, the major categories of these therapies comprised surface-directed passive immunotherapies, adoptive lymphocytic transfer, cancer vaccines, and immune checkpoint blockade (Calinescu et al., 2015; Fecci et al., 2014). For surface-directed passive immunotherapies, the goal is to bind a therapeutic reagent to a specific molecule on the tumor surface in order to block important tumor growth/survival pathways (e.g., EGFR-mediated signaling) or to activate tumoricidal toxins. Effective surface molecules that have shown overexpression in glioblastomas include EGFR, tenascin, transferrin, IL13 and I4 receptors (Calinescu et al., 2015; Fecci et al., 2014). The two major limitations to this methodology are the relative impermeability of the blood brain barrier (BBB) to these large protein constructs, which often require direct injection into the resection cavity and the fact that the response is limited by the half-life of the agent delivered (Fecci et al., 2014; Platten et al., 2016; Sampson et al., 2010). Two other mechanisms likely have also mitigated the efficacy of this methodology, which are the heterogeneity of the surface target expression and the ability of these tumors to adapt to this mode of attack (Furnari et al., 2015; Platten et al., 2016).

Adoptive lymphocyte transfer uses T-cells that are harvested and expanded and sensitized *ex vivo* against glioblastoma for autologous cell transfer back to patients, often with other immune cells, such as dendritic cells (Fecci et al., 2014; Han et al., 2015; Prins et al., 2008; Samaha et al., 2015). To ensure generation of large amounts of functional T-cells, a recent technology development that has shown promise is to genetically modify T-cells to enable expression of a chimeric antigen receptor (CAR), which can bind to tumor antigens in an MHC-unrestricted manner to activate T-cells (Gross et al., 1989; Han et al., 2015).

Also surging is the interest in developing vaccines that are made from antigens (e.g., proteins) expressed almost exclusively by a particular type of cancer cells to activate immune system recognition for selective elimination. Presently, there are five categories of tumor antigen vaccines: (1) *antigen vaccines* that are made from special protein antigens in cancer cells. Since the genetic codes of different cancer cell specific proteins have been uncovered, these vaccines can be made in large quantities; (2) *whole cell vaccines* that are made from the whole cancer cell from the patient, another person, or cancer cells that cultured in the laboratory; (3) *dendritic cell (DC) vaccines* that help the immune system to recognize and attack cancer cells. Often autologous DCs maintained *ex vivo* are pulsed with tumor antigens before injecting back into patients. After stimulation, DCs mature and migrate to draining lymph nodes where they induce immune responses to assault cancer cells; (4) *DNA vaccines* that are made with bits of DNA from cancer cells. Following administration of the vaccines the immune system can be stimulated to destroy the cancer cells; and (5) *anti-idiotypic vaccines* are made of antibodies that detect other antibodies as the antigen and bind to it. The vaccines can stimulate the body to produce antibodies against tumor cells. These strategies have been used individually or in combination with additional molecular manipulations to enhance efficacy, as per the following studies discussed. Similar to human papillomavirus (HPV) and hepatitis B that were found to be causative of cervical and hepatocellular carcinoma, respectively (Benvegnu et al., 1994; Walboomers et al., 1999), potential roles of cytomegalovirus (CMV) in triggering glioblastoma and pediatric glioma were also investigated. In spite of some controversial findings, certain evidence suggested that the viruses may be etiological in the oncogenicity of those tumors (Cobbs, 2013; Mitchell et al., 2008; Wakefield et al., 2015). These possible tumorigenic connections can provide specific antigenic epitopes for developing targeted immune therapies. For example, it was reported that pre-conditioning the vaccine site with a potent recall antigen (i.e., tetanus/diphtheria toxoid: Td) could significantly improve the lymph node homing and potency of tumor-antigen-specific DCs. In randomized patients with glioblastoma who

received pre-conditioning with either mature DCs or Td unilaterally before bilateral vaccination with DCs pulsed with Cytomegalovirus phosphoprotein 65 (pp65: expressing in > 90% of glioblastoma specimens but not in normal brain), those given Td had enhanced DC migration bilaterally and significantly improved survival (Mitchell et al., 2015).

Immune checkpoints are important signaling mechanisms that prevent autoimmune reactions and allow for self-tolerance by decreasing normal T-cell-mediated immune responses (Calinescu et al., 2015). It has become increasingly recognized that tumors, including glioblastoma can damp immune checkpoints to limit host T-cell mediated attack (Fecci et al., 2007; Pardoll, 2012; Platten et al., 2016). Major advances in understanding immune checkpoint inhibition have been made in the treatment of melanoma, where antibodies against CTLA-4 and PD-1 have shown promising results clinically (Hamid et al., 2013; Hodi et al., 2010). Encouraging outcomes have also been reported for preclinical test of immune checkpoint inhibitors in murine models of glioblastoma, and there are several phase I-III trials to determine whether the efficacy may be translated to the clinical realm (Agarwalla et al., 2012; Kim et al., 2017; Wainwright et al., 2014).

2.8. Special considerations for therapeutic delivery to the Spinal cord

Many of the more recent experimental therapies for intracranial gliomas require direct application of these therapies close to the affected area during resection of primary or recurrent gliomas. This is due to the impermeability of the blood-brain barrier (BBB) and blood-spinal cord barrier (BSCB) to large and/or charged (i.e., hydrophilic) molecules such as proteins and the increased effectiveness of the required immune responses following direct injection (Dunn et al., 2012; Hulou et al., 2016; Mitchell et al., 2015). Thus, for therapeutic delivery to SCAs, there have been numerous challenges. First, due to the anatomical fragility of the spinal cord, gross total resection of high grade spinal cord gliomas is often not possible without subjecting patients to neurological deficits. Overall, data to date remains insufficient regarding detailed permeability and metabolic differences between the BSCB and BBB, particularly in terms of unique changes under different diseases and trauma conditions (Bartanusz et al., 2011). Such specific information, if available, would be highly valuable in designing tailored therapies to treat spinal cord tumors and other pathological conditions. Mannitol and other substances have been used to disrupt BSCB in animal models (Prockop et al., 1995). These methods however failed to gain traction in clinical trials, as it was reported that the methods increased the permeability of tumor vasculature by 25%, but increased normal vascular permeability by 10-fold higher, leading to the leakage of proteins, etc. to trigger unwanted systemic effects (Garg et al., 2015; Kroll and Neuwelt, 1998). To overcome uncertainties imposed by the BSCB and BBB, local delivery strategies for conventional therapeutics or stem cells have been extensively investigated. Among the innovative approaches, biodegradable polymers have shown impactful promise in treating both spinal cord and intracranial diseases. Brem et al. first proposed using a biodegradable polymer (poly [bis(p-carboxyphenoxy)]propane-sebacic acid) as a method to administer interstitial chemotherapy in the treatment of primary and recurrent intracranial gliomas (Brem et al., 1995). For therapeutic NSC delivery into the spinal cord, in a joint pioneer study with MIT's Langer Lab we tested a biodegradable polymer construct that was seeded with either murine or human NSCs in the injured rat and non-human primate (i.e., African green monkey) spinal cord, respectively (Teng et al., 2002; Pritchard et al., 2010). The results of these preclinical studies have led to FDA's approval of applying a scaffold alone design as the first implantable therapeutic device for an early phase clinical trial for patients with ASIA acute thoracic spinal cord injury (see details in: <https://clinicaltrials.gov/ct2/show/NCT02138110>). In addition, a report has shown some intriguing results of releasing paclitaxel, a chemotherapeutic agent from ReGel, a thermal gel depot-based delivery system in a rat model of

gliosarcoma (Tyler et al., 2012). We anticipate that future endeavors will concern how to use polymer for controlled release of genetically engineered stem cells or drugs to maximize the initial success we obtained in GDEPT treatment for experimental SCAs (Ropper et al., 2016).

To improve intraparenchymal drug distribution, convection-enhanced delivery (CED) was first presented in 1994 (Bobo et al., 1994) as a method to overcome the diffusion-limited application of chemotherapeutics in the brain. It involves the use of pump connected to an infusion catheter and maintains a pressure gradient, aiming to sustain more diffuse and homogeneous drug concentrations, with results showing improved drug administration in the spinal cord (Endo et al., 2015; Lonser et al., 1998). Interestingly, due to the different anisotropic properties, the gray matter and white matter of the spinal cord exhibit distinct characteristics of drug distribution by CED. Whereas the ratio of the volume of distribution to the volume of infusion in the gray matter was comparable to that of the white matter, drugs remained in the white matter tract and rarely infused into the adjacent gray matter. Conversely, when drugs were injected into the gray matter, they infiltrated laterally into the white matter tract and traveled longitudinally and preferably along the white matter funiculi. At the infusion center, the areas of drug presence were generally larger in the gray matter CED than in the white matter (Endo et al., 2015). The findings have therapeutic implications in the drug delivery to treat spinal cord gliomas, which grow in both the white matter and the gray matter (Ropper et al., 2016).

Lastly, the use of intrathecal delivery has been adopted for the treatment of both brain and spinal cord disorders (Garg et al., 2015; Nance et al., 1995; Sampson et al., 2002; Yu et al., 2013). For long-term release of therapeutic substances, electrical or osmotic pumps connected to an intrathecal catheter have become widespread, especially in the treatment of spasticity or neuropathic pain after spinal cord trauma (Garg et al., 2015; Yu et al., 2013). It should be noted that such systems when used clinically may be susceptible to complications, mostly related to the catheter's physicochemical impact and possible infection (Draulans et al., 2013).

2.9. Summary notes

Although being relatively rare, SCAs are exceedingly difficult clinical entities to treat. This challenge is borne by the fact that many patients present with infiltrative tumors that are not amenable to satisfactory resection or even applying surgical intervention due to the functional eloquence of the axonal tracts and neuronal circuits that carry crucial vital functions of the spinal cord. In our assessment, newly emerged therapies such as genetically engineered stem cell-based GDEPT, direct gene therapy, and targeted immunotherapy are promising domains of therapeutic development that have provided and will continuously offer medical caregivers with more efficacious treatments for patients suffering from high grade SCAs. Importantly, to eventually conquer spinal cord malignant tumors, future interventions must be able to selectively track and ablate the so-called cancer stem cells (CSCs)/tumor survival cells (TSCs). We have shown that CSCs/TSCs of SCAs are more resilient to oncolytic assault than those in brain glioblastoma, as F3.CD NSC implantation plus 5-FC injection was effective in a murine intracranial glioblastoma model but not impactful on C6 SCA in rats (Aboody et al., 2000; Ropper et al., 2016). In addition, hyperthermia preconditioning increased numbers of human glioblastoma cells that expressed CSC/TSC markers and facilitated their engrafting in the adult rat spinal cord (Zeng et al., 2016). Therefore, future therapeutic designs for SCAs should factor in mechanisms that can specifically target the most critical features of the disease in regards of tumorigenesis, malignant grade, lethality, functional anatomy of the spinal cord, pharmacokinetics, and synergistic combination of treatment modalities.

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There is no conflict of interest to disclose. FDA device and drug status are not applicable for this paper.

References

- Abd-El-Barr, M.M., Huang, K.T., Chi, J.H., 2016. Infiltrating spinal cord astrocytomas: Epidemiology, diagnosis, treatments and future directions. *J. Clin. Neurosci.* 29, 15–20.
- Abdel-Wahab, M., Etuk, B., Palermo, J., Shirato, H., Kresl, J., Yapicier, O., Walker, G., Scheithauer, B.W., Shaw, E., Lee, C., Curran, W., Thomas, T., Markoe, A., 2006. Spinal cord gliomas: A multi-institutional retrospective analysis. *Int. J. Radiat. Oncol. Biol. Phys.* 64, 1060–1071.
- Aboody, K.S., Brown, A., Rainov, N.G., Bower, K.A., Liu, S., Yang, W., Small, J.E., Herrlinger, U., Ourednik, V., Black, P.M., Breakefield, X.O., Snyder, E.Y., 2000. Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. *Proc. Natl. Acad. Sci. U. S. A.* 97, 12846–12851.
- Aboody, K., Capela, A., Niazi, N., Stern, J.H., Temple, S., 2011. Translating stem cell studies to the clinic for CNS repair: current state of the art and the need for a Rosetta stone. *Neuron* 70, 597–613.
- Agarwalla, P., Barnard, Z., Fecci, P., Dranoff, G., Curry Jr., W.T., 2012. Sequential immunotherapy by vaccination with GM-CSF-expressing glioma cells and CTLA-4 blockade effectively treats established murine intracranial tumors. *J. Immunother.* 35, 385–389.
- Babu, R., Karikari, I.O., Owens, T.R., Bagley, C.A., 2014. Spinal cord astrocytomas: a modern 20-year experience at a single institution. *Spine (Phila Pa 1976)* 39, 533–540.
- Barrangou, R., Fremaux, C., Deveau, H., Richards, M., Boyaval, P., Moineau, S., Romero, D.A., Horvath, P., 2007. CRISPR provides acquired resistance against viruses in prokaryotes. *Science* 315, 1709–1712.
- Bartanusz, V., Jezova, D., Alajajian, B., Digicaylioglu, M., 2011. The blood-spinal cord barrier: morphology and clinical implications. *Ann. Neurol.* 70, 194–206.
- Bender, S., Tang, Y., Lindroth, A.M., Hovestadt, V., Jones, D.T., Kool, M., Zapata, M., Northcott, P.A., Sturm, D., Wang, W., Radlwimmer, B., Hofjeldt, J.W., Truffaux, N., Castel, D., Schubert, S., Ryzhova, M., Seker-Cin, H., Gronych, J., Johann, P.D., Stark, S., Meyer, J., Milde, T., Schuhmann, M., Ebinger, M., Monoranu, C.M., Ponnuswami, A., Chen, S., Jones, C., Witt, O., Collins, V.P., von Deimling, A., Jabado, N., Puget, S., Grill, J., Helin, K., Korshunov, A., Lichter, P., Monje, M., Plass, C., Cho, Y.J., Pfister, S.M., 2013. Reduced H3K27me3 and DNA hypomethylation are major drivers of gene expression in K27M mutant pediatric high-grade gliomas. *Cancer Cell* 24, 660–672.
- Benvegnù, L., Fattovich, G., Noventa, F., Tremolada, F., Chemello, L., Cecchetto, A., Alberti, A., 1994. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. A prospective study. *Cancer* 74, 2442–2448.
- Bjerke, L., Mackay, A., Nandhabalan, M., Burford, A., Jury, A., Popov, S., Bax, D.A., Carvalho, D., Taylor, K.R., Vinci, M., Bajrami, I., McGonnell, I.M., Lord, C.J., Reis, R.M., Hargrave, D., Ashworth, A., Workman, P., Jones, C., 2013. Histone H3.3 mutations drive pediatric glioblastoma through upregulation of MYCN. *Cancer Discov* 3, 512–519.
- Bobo, R.H., Laske, D.W., Akbasak, A., Morrison, P.F., Dedrick, R.L., Oldfield, E.H., 1994. Convection-enhanced delivery of macromolecules in the brain. *Proc. Natl. Acad. Sci. U. S. A.* 91, 2076–2080.
- Brem, H., Piantadosi, S., Burger, P.C., Walker, M., Selker, R., Vick, N.A., Black, K., Sisti, M., Brem, S., Mohr, G., et al., 1995. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet* 345, 1008–1012.
- Burnet, F.M., 1967. Immunological aspects of malignant disease. *Lancet* 1, 1171–1174.
- Calinescu, A.A., Kamran, N., Baker, G., Mineharu, Y., Lowenstein, P.R., Castro, M.G., 2015. Overview of current immunotherapeutic strategies for glioma. *Immunotherapy* 7, 1073–1104.
- Caplan, J., Pradilla, G., Hdeib, A., Tyler, B.M., Legnani, F.G., Bagley, C.A., Brem, H., Jallo, G., 2006. A novel model of intramedullary spinal cord tumors in rats: functional progression and histopathological characterization. *Neurosurgery* 59, 193–200 discussion 193–200.
- Chamberlain, M.C., 2008. Temozolomide for recurrent low-grade spinal cord gliomas in adults. *Cancer* 113, 1019–1024.
- Chamberlain, M.C., Johnston, S.K., 2011. Recurrent spinal cord glioblastoma: salvage therapy with bevacizumab. *J. Neuro-Oncol.* 102, 427–432.
- Chamberlain, M.C., Tredway, T.L., 2011. Adult primary intradural spinal cord tumors: a review. *Curr Neurol Neurosci Rep* 11, 320–328.
- Chan, J.A., Krichevsky, A.M., Kosik, K.S., 2005. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Res.* 65, 6029–6033.
- Chen, Y., Gorski, D.H., 2008. Regulation of angiogenesis through a microRNA (miR-130a)

- that down-regulates antiangiogenic homeobox genes GAX and HOXA5. *Blood* 111, 1217–1226.
- Cheney, I.W., Johnson, D.E., Vaillancourt, M.-T., Avanzini, J., Morimoto, A., Demers, G.W., Wills, K.N., Shabram, P.W., Bolen, J.B., Tavtigian, S.V., Bookstein, R., 1998. Suppression of Tumorigenicity of Glioblastoma Cells by Adenovirus-mediated $\langle em \rangle$ MMAC1/PTEN $\langle /em \rangle$ Gene Transfer. *Cancer Res.* 58, 2331–2334.
- Chulpanova, D.S., Kitaeva, K.V., Tazetdinova, L.G., James, V., Rizvanov, A.A., Solovyeva, V.V., 2018. Application of Mesenchymal Stem Cells for Therapeutic Agent Delivery in Anti-tumor Treatment. *Front. Pharmacol.* 9, 259.
- Chung, T., Na, J., Kim, Y.I., Chang, D.Y., Kim, Y.I., Kim, H., Moon, H.E., Kang, K.W., Lee, D.S., Chung, J.K., Kim, S.S., Suh-Kim, H., Paek, S.H., Youn, H., 2016. Dihydropyrimidine Dehydrogenase Is a Prognostic Marker for Mesenchymal Stem Cell-Mediated Cytosine Deaminase Gene and 5-Fluorocytosine Prodrug Therapy for the Treatment of Recurrent Gliomas. *Theranostics* 6, 1477–1490.
- Cobbs, C.S., 2013. Cytomegalovirus and brain tumor: epidemiology, biology and therapeutic aspects. *Curr. Opin. Oncol.* 25, 682–688.
- Corradini, S., Hadi, I., Hankel, V., Ertl, L., Ganswindt, U., Belka, C., Niyazi, M., 2016. Radiotherapy of spinal cord gliomas: A retrospective mono-institutional analysis. *Strahlenther. Onkol.* 192, 139–145.
- Davies, H., Bignell, G.R., Cox, C., Stephens, P., Edkins, S., Clegg, S., Teague, J., Woffendin, H., Garnett, M.J., Bottomley, W., Davis, N., Dicks, E., Ewing, R., Floyd, Y., Gray, K., Hall, S., Hawes, R., Hughes, J., Kosmidou, V., Menzies, A., Mould, C., Parker, A., Stevens, C., Watt, S., Hooper, S., Wilson, R., Jayatilake, H., Gusterson, B.A., Cooper, C., Shipley, J., Hargrave, D., Pritchard-Jones, K., Maitland, N., Chenevix-Trench, G., Riggins, G.J., Bigner, D.D., Palmieri, G., Cossu, A., Flanagan, A., Nicholson, A., Ho, J.W., Leung, S.Y., Yuen, S.T., Weber, B.L., Seigler, H.F., Darrow, T.L., Paterson, H., Marais, R., Marshall, C.J., Wooster, R., Stratton, M.R., Futreal, P.A., 2002. Mutations of the BRAF gene in human cancer. *Nature* 417, 949–954.
- Deletis, V., Sala, F., 2008. Intraoperative neurophysiological monitoring of the spinal cord during spinal cord and spine surgery: a review focus on the corticospinal tracts. *Clin. Neurophysiol.* 119, 248–264.
- Doll, R., Kinlen, L., 1970. Immunosurveillance and cancer: epidemiological evidence. *Br. Med. J.* 4, 420–422.
- Draulans, N., Vermeersch, K., Degraeuwe, B., Meurrens, T., Peers, K., Nuttin, B., Kiekens, C., 2013. Intrathecal baclofen in multiple sclerosis and spinal cord injury: complications and long-term dosage evolution. *Clin. Rehabil.* 27, 1137–1143.
- Dunn, G.P., Fecci, P.E., Curry, W.T., 2012. Cancer immunoeediting in malignant glioma. *Neurosurgery* 71, 201–222 discussion 222–203.
- Endo, T., Fujii, Y., Sugiyama, S.I., Zhang, R., Ogita, S., Funamoto, K., Saito, R., Tominaga, T., 2015. Properties of convective delivery in spinal cord gray matter: laboratory investigation and computational simulations. *J. Neurosurg Spine* 1–8.
- Epstein, F.J., Farmer, J.P., Freed, D., 1992. Adult intramedullary astrocytomas of the spinal cord. *J. Neurosurg.* 77, 355–359.
- Fakhreddine, M.H., Mahajan, A., Penas-Prado, M., Weinberg, J., McCutcheon, I.E., Puduvalli, V., Brown, P.D., 2013. Treatment, prognostic factors, and outcomes in spinal cord astrocytomas. *Neuro-Oncology* 15, 406–412.
- Fecci, P.E., Ochiai, H., Mitchell, D.A., Grossi, P.M., Sweeney, A.E., Archer, G.E., Cummings, T., Allison, J.P., Bigner, D.D., Sampson, J.H., 2007. Systemic CTLA-4 blockade ameliorates glioma-induced changes to the CD4+ T cell compartment without affecting regulatory T-cell function. *Clin. Cancer Res.* 13, 2158–2167.
- Fecci, P.E., Heimberger, A.B., Sampson, J.H., 2014. Immunotherapy for primary brain tumors: no longer a matter of privilege. *Clin. Cancer Res.* 20, 5620–5629.
- Friedmann, T., Roblin, R., 1972. Gene therapy for human genetic disease? *Science* 178, 648–649.
- Furlan, J.C., Fehlings, M.G., Halliday, W., Krassioukov, A.V., 2003. Autonomic dysreflexia associated with intramedullary astrocytoma of the spinal cord. *Lancet Oncol.* 4, 574–575.
- Furnari, F.B., Cloughesy, T.F., Cavenee, W.K., Mischel, P.S., 2015. Heterogeneity of epidermal growth factor receptor signalling networks in glioblastoma. *Nat. Rev. Cancer* 15, 302–310.
- Fuxe, J., Akusjarvi, G., Goike, H.M., Roos, G., Collins, V.P., Pettersson, R.F., 2000. Adenovirus-mediated overexpression of p15INK4B inhibits human glioma cell growth, induces replicative senescence, and inhibits telomerase activity similarly to p16INK4A. *Cell Growth Differ.* 11, 373–384.
- Garces-Ambrossi, G.L., McGirt, M.J., Mehta, V.A., Sciubba, D.M., Witham, T.F., Bydon, A., Wolinsky, J.P., Jallo, G.I., Gokaslan, Z.L., 2009. Factors associated with progression-free survival and long-term neurological outcome after resection of intramedullary spinal cord tumors: analysis of 101 consecutive cases. *J. Neurosurg Spine* 11, 591–599.
- Garg, T., Bhandari, S., Rath, G., Goyal, A.K., 2015. Current strategies for targeted delivery of bio-active drug molecules in the treatment of brain tumor. *J. Drug Target.* 23, 865–887.
- Gross, G., Waks, T., Eshhar, Z., 1989. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. *Proc. Natl. Acad. Sci. U. S. A.* 86, 10024–10028.
- Grosso, S., Doyen, J., Parks, S.K., Bertero, T., Paye, A., Cardinaud, B., Gounon, P., Lacas-Gervais, S., Noël, A., Pouyssegur, J., Barbry, P., Mazure, N.M., Mari, B., 2013. MiR-210 promotes a hypoxic phenotype and increases radioresistance in human lung cancer cell lines. *Cell Death Dis.* 4 e544.
- Guss, Z.D., Moningi, S., Jallo, G.I., Cohen, K.J., Wharam, M.D., Terezakis, S.A., 2013. Management of pediatric spinal cord astrocytomas: outcomes with adjuvant radiation. *Int. J. Radiat. Oncol. Biol. Phys.* 85, 1307–1311.
- Hamid, O., Robert, C., Daud, A., Hodi, F.S., Hwu, W.J., Kefford, R., Wolchok, J.D., Hersey, P., Joseph, R.W., Weber, J.S., Dronca, R., Gangadhar, T.C., Patnaik, A., Zarour, H., Joshua, A.M., Gergich, K., Ellassaiss-Schaap, J., Algazi, A., Mateus, C., Boasberg, P., Tume, P.C., Chmielowski, B., Ebbinghaus, S.W., Li, X.N., Kang, S.P., Ribas, A., 2013. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N. Engl. J. Med.* 369, 134–144.
- Han, J., Chu, J., Keung Chan, W., Zhang, J., Wang, Y., Cohen, J.B., Victor, A., Meisen, W.H., Kim, S.H., Grandi, P., Wang, Q.E., He, X., Nakano, I., Chiozza, E.A., Glorioso Jr, J.C., Kaur, B., Caligiuri, M.A., Yu, J., 2015. CAR-Engineered NK Cells Targeting Wild-Type EGFR and EGFRvIII Enhance Killing of Glioblastoma and Patient-Derived Glioblastoma Stem Cells. *Sci. Rep.* 5, 11483.
- Han, I.B., Kim, M., Lee, S.H., Kim, J.K., Kim, S.H., Chang, J.H., Teng, Y.D., 2016. Down-regulation of MicroRNA-126 in Glioblastoma and its Correlation with Patient Prognosis: A Pilot Study. *Anticancer Res.* 36, 6691–6697.
- Hegi, M.E., Diserens, A.C., Gorlia, T., Hamou, M.F., de Tribolet, N., Weller, M., Kros, J.M., Hainfellner, J.A., Mason, W., Mariani, L., Bromberg, J.E., Hau, P., Mirimanoff, R.O., Cairncross, J.G., Janzer, R.C., Stupp, R., 2005. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N. Engl. J. Med.* 352, 997–1003.
- Heo, D.H., Kim, S.H., Yang, K.M., Cho, Y.J., Kim, K.N., Yoon, D.H., Kang, T.C., 2012. A histopathological diagnostic marker for human spinal astrocytoma: expression of glial fibrillary acidic protein-delta. *J. Neuro-Oncol.* 108, 45–52.
- Hermansen, S.K., Dahlrot, R.H., Nielsen, B.S., Hansen, S., Kristensen, B.W., 2013. MiR-21 expression in the tumor cell compartment holds unfavorable prognostic value in gliomas. *J. Neuro-Oncol.* 111, 71–81.
- Hodi, F.S., O'Day, S.J., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., Gonzalez, R., Robert, C., Schadendorf, D., Hassel, J.C., Akerley, W., van den Eertwegh, A.J., Lutzky, J., Lorigan, P., Vaubel, J.M., Linette, G.P., Hogg, D., Ottensmeier, C.H., Lebbe, C., Peschel, C., Quirt, I., Clark, J.I., Wolchok, J.D., Weber, J.S., Tian, J., Yellin, M.J., Nichol, G.M., Hoos, A., Urba, W.J., 2010. Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* 363, 711–723.
- Horbinski, C., Nikiforova, M.N., Hagenkord, J.M., Hamilton, R.L., Pollack, I.F., 2012. Interplay among BRAF, p16, p53, and MIB1 in pediatric low-grade gliomas. *Neuro-Oncology* 14, 777–789.
- Horvath, P., Barrangou, R., 2010. CRISPR/Cas, the immune system of bacteria and archaea. *Science* 327, 167–170.
- Hsu, W., Situ, I.M., Pradilla, G., Gokaslan, Z.L., Jallo, G.I., Gallia, G.L., 2012. Animal model of intramedullary spinal cord glioma using human glioblastoma multiforme neurospheres. *J. Neurosurg Spine* 16, 315–319.
- Huillard, E., Hashizume, R., Phillips, J.J., Griveau, A., Ihrle, R.A., Aoki, Y., Nicolaidis, T., Perry, A., Waldman, T., McMahon, M., Weiss, W.A., Petrisch, C., James, C.D., Rowitch, D.H., 2012. Cooperative interactions of BRAFV600E kinase and CDKN2A locus deficiency in pediatric malignant astrocytoma as a basis for rational therapy. *Proc. Natl. Acad. Sci. U. S. A.* 109, 8710–8715.
- Hulou, M.M., Cho, C.F., Chiozza, E.A., Bjerkvig, R., 2016. Experimental therapies: gene therapies and oncolytic viruses. *Handb. Clin. Neurol.* 134, 183–197.
- Ichimura, K., Bolin, M.B., Goike, H.M., Schmidt, E.E., Moshref, A., Collins, V.P., 2000. Deregulation of the p14ARF/MDM2/p53 pathway is a prerequisite for human astrocytic gliomas with G1-S transition control gene abnormalities. *Cancer Res.* 60, 417–424.
- Iwade, Y., Mochizuki, S., Fujimoto, S., Namba, H., Sakiyama, S., Tagawa, M., Yamaura, A., 2000. Alteration of CDKN2/p16 in human astrocytic tumors is related with increased susceptibility to antimetabolite anticancer agents. *Int. J. Oncol.* 17, 501–505.
- Jang, C.W., Shibata, Y., Starmer, J., Yee, D., Magnuson, T., 2015. Histone H3.3 maintains genome integrity during mammalian development. *Genes Dev.* 29, 1377–1392.
- Jiang, L., Mao, P., Song, L., Wu, J., Huang, J., Lin, C., Yuan, J., Qu, L., Cheng, S.Y., Li, J., 2010. miR-182 as a prognostic marker for glioma progression and patient survival. *Am. J. Pathol.* 177, 29–38.
- Jiang, H., Yu, W.-W., Wang, L.-L., Peng, Y., 2015. miR-130a acts as a potential diagnostic biomarker and promotes gastric cancer migration, invasion and proliferation by targeting RUNX3. *Oncol. Rep.* 34, 1153–1161.
- Jo, S.H., Son, M.K., Koh, H.J., Lee, S.M., Song, I.H., Kim, Y.O., Lee, Y.S., Jeong, K.S., Kim, W.B., Park, J.W., Song, B.J., Huh, T.L., 2001. Control of mitochondrial redox balance and cellular defense against oxidative damage by mitochondrial NADP+ -dependent isocitrate dehydrogenase. *J. Biol. Chem.* 276, 16168–16176.
- Johannessen, C.M., Reczek, E.E., James, M.F., Brems, H., Legius, E., Cichowski, K., 2005. The NF1 tumor suppressor critically regulates TSC2 and mTOR. *Proc. Natl. Acad. Sci. U. S. A.* 102, 8573–8578.
- Jones, D.T., Kocialkowski, S., Liu, L., Pearson, D.M., Backlund, L.M., Ichimura, K., Collins, V.P., 2008. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. *Cancer Res.* 68, 8673–8677.
- Jyothirmayi, R., Madhavan, J., Nair, M.K., Rajan, B., 1997. Conservative surgery and radiotherapy in the treatment of spinal cord astrocytoma. *J. Neuro-Oncol.* 33, 205–211.
- Kaley, T.J., Mondesire-Crump, I., Gavrilovic, I.T., 2012. Temozolomide or bevacizumab for spinal cord high-grade gliomas. *J. Neuro-Oncol.* 109, 385–389.
- Kang, H.-J., Cui, Y., Yin, H., Scheid, A., Hendricks, W.P., Schmidt, J., Sekulic, A., Kong, D., Trent, J.M., Gokhale, V., 2016. A pharmacological chaperone molecule induces cancer cell death by restoring tertiary DNA structures in mutant hTERT promoters. *J. Am. Chem. Soc.* 138, 13673–13692.
- Karikari, I.O., Nimjee, S.M., Hodges, T.R., Cutrell, E., Hughes, B.D., Powers, C.J., Mehta, A.I., Hardin, C., Bagley, C.A., Isaacs, R.E., Haglund, M.M., Friedman, A.H., 2011. Impact of tumor histology on resectability and neurological outcome in primary intramedullary spinal cord tumors: a single-center experience with 102 patients. *Neurosurgery* 68, 188–197 discussion 197.
- Karikari, I.O., Nimjee, S.M., Hodges, T.R., Cutrell, E., Hughes, B.D., Powers, C.J., Mehta, A.I., Hardin, C., Bagley, C.A., Isaacs, R.E., Haglund, M.M., Friedman, A.H., 2015. Impact of tumor histology on resectability and neurological outcome in primary intramedullary spinal cord tumors: a single-center experience with 102 patients.

- Neurosurgery 76 (Suppl 1), S4–S13 discussion S13.
- Karsy, M., Guan, J., Sivakumar, W., Neil, J.A., Schmidt, M.H., Mahan, M.A., 2015. The genetic basis of intradural spinal tumors and its impact on clinical treatment. *Neurosurg. Focus.* 39, E3.
- Kefas, B., Comeau, L., Erdle, N., Montgomery, E., Amos, S., Purow, B., 2010. Pyruvate kinase M2 is a target of the tumor-suppressive microRNA-326 and regulates the survival of glioma cells. *Neuro-Oncology* 12, 1102–1112.
- Kim, S.K., Cargioli, T.G., Machluf, M., Yang, W., Sun, Y., Al-Hashem, R., Kim, S.U., Black, P.M., Carroll, R.S., 2005. PEX-producing human neural stem cells inhibit tumor growth in a mouse glioma model. *Clin. Cancer Res.* 11, 5965–5970.
- Kim, W.H., Yoon, S.H., Kim, C.Y., Kim, K.J., Lee, M.M., Choe, G., Kim, I.A., Kim, J.H., Kim, Y.J., Kim, H.J., 2011. Temozolomide for malignant primary spinal cord glioma: an experience of six cases and a literature review. *J. Neuro-Oncol.* 101, 247–254.
- Kim, J.E., Patel, M.A., Mangraviti, A., Kim, E.S., Theodoros, D., Velarde, E., Liu, A., Sankey, E.W., Tam, A., Xu, H., Mathios, D., Jackson, C.M., Harris-Bookman, S., Garzon-Muvidi, T., Sheu, M., Martin, A.M., Tyler, B.M., Tran, P.T., Ye, X., Olivi, A., Taube, J.M., Burger, P.C., Drake, C.G., Brem, H., Pardoll, D.M., Lim, M., 2017. Combination Therapy with Anti-PD-1, Anti-TIM-3, and Focal Radiation Results in Regression of Murine Gliomas. *Clin. Cancer Res.* 23, 124–136.
- Konar, S.K., Bir, S.C., Maiti, T.K., Nanda, A., 2017. A systematic review of overall survival in pediatric primary glioblastoma multiforme of the spinal cord. *J. Neurosurg. Pediatr.* 19, 239–248.
- Krassioukov, A., Warburton, D.E., Teasell, R., Eng, J.J., 2009. A systematic review of the management of autonomic dysreflexia after spinal cord injury. *Arch. Phys. Med. Rehabil.* 90, 682–695.
- Krimpenfort, P., Ijpenberg, A., Song, J.Y., van der Valk, M., Nawijn, M., Zevenhoven, J., Berns, A., 2007. p15Ink4b is a critical tumour suppressor in the absence of p16Ink4a. *Nature* 448, 943–946.
- Kroll, R.A., Neuwelt, E.A., 1998. Outwitting the blood-brain barrier for therapeutic purposes: osmotic opening and other means. *Neurosurgery* 42, 1083–1099 discussion 1099–1100.
- Kutluk, T., Varan, A., Kafali, C., Hayran, M., Soylemezoglu, F., Zorlu, F., Aydin, B., Yalcin, B., Akyuz, C., Buyukpamukcu, M., 2015. Pediatric intramedullary spinal cord tumors: a single center experience. *Eur. J. Paediatr. Neurol.* 19, 41–47.
- Lammering, G., Hewit, T.H., Valerie, K., Contessa, J.N., Amorino, G.P., Dent, P., Schmidt-Ullrich, R.K., 2003. EGFRvIII-mediated radioresistance through a strong cytoprotective response. *Oncogene* 22, 5545–5553.
- Liu, D., Liu, Z., Condouris, S., Xing, M., 2007. BRAF V600E Maintains Proliferation, Transformation, and Tumorigenicity of BRAF-Mutant Papillary Thyroid Cancer Cells. *J. Clin. Endocrinol. Metab.* 92, 2264–2271.
- Liu, Q., Zou, R., Zhou, R., Gong, C., Wang, Z., Cai, T., Tan, C., Fang, J., 2015. miR-155 Regulates Glioma Cells Invasion and Chemosensitivity by p38 Isoforms In Vitro. *J. Cell. Biochem.* 116, 1213–1221.
- Llorens-Bobadilla, E., Martin-Villalba, A., 2017. Adult NSC diversity and plasticity: the role of the niche. *Curr. Opin. Neurobiol.* 42, 68–74.
- Lonser, R.R., Gogate, N., Morrison, P.F., Wood, J.D., Oldfield, E.H., 1998. Direct convective delivery of macromolecules to the spinal cord. *J. Neurosurg.* 89, 616–622.
- Lötsch, D., Ghanim, B., Laaber, M., Wurm, G., Weis, S., Lenz, S., Webersinke, G., Pichler, J., Berger, W., Spiegel-Kreinecker, S., 2013. Prognostic significance of telomerase-associated parameters in glioblastoma: effect of patient age. *Neuro-Oncology* 15, 423–432.
- Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., Burger, P.C., Jouvet, A., Scheithauer, B.W., Kleihues, P., 2007. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol.* 114, 97–109.
- Louis, D.N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W.K., Ohgaki, H., Wiestler, O.D., Kleihues, P., Ellison, D.W., 2016. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 131, 803–820.
- Maeder, M.L., Gersbach, C.A., 2016. Genome-editing Technologies for Gene and Cell Therapy. *Mol. Ther.* 24, 430–446.
- Maguire, C.A., Ramirez, S.H., Merkel, S.F., Sena-Esteves, M., Breakefield, X.O., 2014. Gene therapy for the nervous system: challenges and new strategies. *Neurotherapeutics* 11, 817–839.
- McCool, F.D., 2012. Chapter 99. Diseases of the diaphragm, chest wall, pleura, and mediastinum. In: Cecil, R.L.F., Goldman, L., Schafer, A.I. (Eds.), *Goldman's Cecil Medicine*. Elsevier Saunders, Philadelphia, PA, pp. 603.
- McGirt, M.J., Goldstein, I.M., Chaichana, K.L., Tobias, M.E., Kothbauer, K.F., Jallo, G.I., 2008. Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients. *Neurosurgery* 63, 55–60 discussion 60–51.
- McGirt, M.J., Mukherjee, D., Chaichana, K.L., Than, K.D., Weingart, J.D., Quinones-Hinojosa, A., 2009. Association of surgically acquired motor and language deficits on overall survival after resection of glioblastoma multiforme. *Neurosurgery* 65, 463–469 discussion 469–470.
- Medawar, P.B., 1948. Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. *Br. J. Exp. Pathol.* 29, 58–69.
- Micallef, J., Taccone, M., Mukherjee, J., Croul, S., Busby, J., Moran, M.F., Guha, A., 2009. Epidermal growth factor receptor variant III-induced glioma invasion is mediated through myristoylated alanine-rich protein kinase C substrate overexpression. *Cancer Res.* 69, 7548–7556.
- Milano, M.T., Johnson, M.D., Sul, J., Mohile, N.A., Korones, D.N., Okunieff, P., Walter, K.A., 2010. Primary spinal cord glioma: a Surveillance, Epidemiology, and End Results database study. *J. Neuro-Oncol.* 98, 83–92.
- Minehan, K.J., Brown, P.D., Scheithauer, B.W., Krauss, W.E., Wright, M.P., 2009. Prognosis and treatment of spinal cord astrocytoma. *Int. J. Radiat. Oncol. Biol. Phys.* 73, 727–733.
- Mistry, M., Zhukova, N., Merico, D., Rakopoulos, P., Krishnatry, R., Shago, M., Stavropoulos, J., Alon, N., Pole, J.D., Ray, P.N., Navickiene, V., Mangerel, J., Remke, M., Buczkowicz, P., Ramaswamy, V., Stucklin, A.G., Li, M., Young, E.J., Zhang, C., Castelo-Branco, P., Bakry, D., Laughlin, S., Shlien, A., Chan, J., Ligon, K.L., Rutka, J.T., Dirks, P.B., Taylor, M.D., Greenberg, M., Malkin, D., Huang, A., Bouffet, E., Hawkins, C.E., Tabori, U., 2015. BRAF Mutation and CDKN2A Deletion Define a Clinically Distinct Subgroup of Childhood Secondary High-Grade Glioma. *J. Clin. Oncol.* 33, 1015–1022.
- Mitchell, D.A., Xie, W., Schmittling, R., Learn, C., Friedman, A., McLendon, R.E., Sampson, J.H., 2008. Sensitive detection of human cytomegalovirus in tumors and peripheral blood of patients diagnosed with glioblastoma. *Neuro-Oncology* 10, 10–18.
- Mitchell, D.A., Batich, K.A., Gunn, M.D., Huang, M.N., Sanchez-Perez, L., Nair, S.K., Congdon, K.L., Reap, E.A., Archer, G.E., Desjardins, A., Friedman, A.H., Friedman, H.S., Herndon 2nd, J.E., Coan, A., McLendon, R.E., Reardon, D.A., Vredenburgh, J.J., Bigner, D.D., Sampson, J.H., 2015. Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients. *Nature* 519, 366–369.
- Nagaishi, M., Nobusawa, S., Yokoo, H., Sugiura, Y., Tsuda, K., Tanaka, Y., Suzuki, K., Hyodo, A., 2016. Genetic mutations in high grade gliomas of the adult spinal cord. *Brain Tumor Pathol* 33, 267–269.
- Nair, D., Kumaraswamy, V.M., Braver, D., Kilbride, R.D., Borges, L.F., Simon, M.V., 2014. Dorsal column mapping via phase reversal method: the refined technique and clinical applications. *Neurosurgery* 74, 437–446 discussion 446.
- Nance, P., Schryvers, O., Schmidt, B., Dubo, H., Loveridge, B., Fewer, D., 1995. Intrathecal baclofen therapy for adults with spinal spasticity: therapeutic efficacy and effect on hospital admissions. *Can J Neurol Sci* 22, 22–29.
- Oda, K., Matsuoka, Y., Funahashi, A., Kitano, H., 2005. A comprehensive pathway map of epidermal growth factor receptor signaling. *Mol. Syst. Biol.* 1, 2005.0010.
- O'Duibhir, E., Carragher, N.O., Pollard, S.M., 2017. Accelerating glioblastoma drug discovery: Convergence of patient-derived models, genome editing and phenotypic screening. *Mol. Cell. Neurosci.* 80, 198–207.
- Osborn, J.W., Taylor, R.F., Schramm, L.P., 1990. Chronic cervical spinal cord injury and autonomic hyperreflexia in rats. *Am. J. Phys.* 258, R169–R174.
- Ostrom, Q.T., Bauchet, L., Davis, F.G., Deltoro, I., Fisher, J.L., Langer, C.E., Pekmezci, M., Schwartzbaum, J.A., Turner, M.C., Walsh, K.M., Wrensch, M.R., Barnholtz-Sloan, J.S., 2014a. The epidemiology of glioma in adults: a "state of the science" review. *Neuro-Oncology* 16, 896–913.
- Ostrom, Q.T., Gittleman, H., Liao, P., Rouse, C., Chen, Y., Dowling, J., Wolinsky, Y., Kruchko, C., Barnholtz-Sloan, J., 2014b. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. *Neuro-Oncology* 16 (Suppl. 4), iv1–vi3.
- Pardoll, D.M., 2012. The blockade of immune checkpoints in cancer immunotherapy. *Nat. Rev. Cancer* 12, 252–264.
- Park, S.M., Choi, E.Y., Bae, M., Kim, S., Park, J.B., Yoo, H., Choi, J.K., Kim, Y.J., Lee, S.H., Kim, I.H., 2016. Histone variant H3F3A promotes lung cancer cell migration through intronic regulation. *Nat. Commun.* 7.
- Parsa, A.T., Chi, J.H., Acosta Jr., F.L., Ames, C.P., McCormick, P.C., 2005. Intramedullary spinal cord tumors: molecular insights and surgical innovation. *Clin. Neurosurg.* 52, 76–84.
- Penman, C.L., Faulkner, C., Lowis, S.P., Kurian, K.M., 2015. Current Understanding of BRAF Alterations in Diagnosis, Prognosis, and Therapeutic Targeting in Pediatric Low-Grade Gliomas. *Front. Oncol.* 5, 54.
- Platten, M., Bunse, L., Wick, W., Bunse, T., 2016. Concepts in glioma immunotherapy. *Cancer Immunol. Immunother.* 65, 1269–1275.
- Portnow, J., Synold, T.W., Badie, B., Tirughana, R., Lacey, S.F., D'Apuzzo, M., Metz, M.Z., Najbauer, J., Bedell, V., Vo, T., Gutova, M., Frankel, P., Chen, M., Aboody, K.S., 2017. Neural Stem Cell-Based Anticancer Gene Therapy: A First-in-Human Study in Recurrent High-Grade Glioma Patients. *Clin. Cancer Res.* 23, 2951–2960.
- Prins, R.M., Shu, C.J., Radu, C.G., Vo, D.D., Khan-Farooqi, H., Soto, H., Yang, M.Y., Lin, M.S., Shelly, S., Witte, O.N., Ribas, A., Liau, L.M., 2008. Anti-tumor activity and trafficking of self, tumor-specific T cells against tumors located in the brain. *Cancer Immunol. Immunother.* 57, 1279–1289.
- Pritchard, C.D., Slotkin, J.R., Yu, D., Dai, H., Lawrence, M.S., Bronson, R.T., Reynolds, F.M., Teng, Y.D., Woodard, E.J., Langer, R.S., 2010. Establishing a model spinal cord injury in the African green monkey for the preclinical evaluation of biodegradable polymer scaffolds seeded with human neural stem cells. *J. Neurosci. Methods* 188, 258–269.
- Prockop, L.D., Naidu, K.A., Binard, J.E., Ransohoff, J., 1995. Selective permeability of [3H]-D-mannitol and [14C]-carboxyl-inulin across the blood-brain barrier and blood-spinal cord barrier in the rabbit. *J. Spinal Cord Med* 18, 221–226.
- Qiu, S., Lin, S., Hu, D., Feng, Y., Tan, Y., Peng, Y., 2013. Interactions of miR-323/miR-326/miR-329 and miR-130a/miR-155/miR-210 as prognostic indicators for clinical outcome of glioblastoma patients. *J. Transl. Med.* 11, 10.
- Que, T., Song, Y., Liu, Z., Zheng, S., Long, H., Li, Z., Liu, Y., Wang, G., Liu, Y., Zhou, J., Zhang, X., Fang, W., Qi, S., 2015. Decreased miRNA-637 is an unfavorable prognosis marker and promotes glioma cell growth, migration and invasion via direct targeting Akt1. *Oncogene* 34, 4952.
- Raco, A., Esposito, V., Lenzi, J., Piccirilli, M., Delfini, R., Cantore, G., 2005. Long-term follow-up of intramedullary spinal cord tumors: a series of 202 cases. *Neurosurgery* 56, 972–981 discussion 972–981.
- Rahman, M., Abbattamatteo, J., De Leo, E.K., Kubilis, P.S., Vaziri, S., Bova, F., Sayour, E., Mitchell, D., Quinones-Hinojosa, A., 2017. The effects of new or worsened post-operative neurological deficits on survival of patients with glioblastoma. *J. Neurosurg.* 127, 123–131.
- Reddy, R.J., Gajadhar, A.S., Swenson, E.J., Rothenberg, D.A., Curran, T.G., White, F.M., 2016. Early signaling dynamics of the epidermal growth factor receptor. *Proc. Natl.*

- Acad. Sci. 113, 3114–3119.
- Ren, T.J., Wang, Z.C., Zhang, Y.Z., Li, D., Wang, H.Y., Li, Z.Z., 2010. Establishment of intramedullary spinal cord glioma model in rats. *Chin. Med. J.* 123, 2580–2585.
- Rodrigues, G.B., Waldron, J.N., Wong, C.S., Laperriere, N.J., 2000. A retrospective analysis of 52 cases of spinal cord glioma managed with radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 48, 837–842.
- Ropper, A.E., Zeng, X., Haragopal, H., Anderson, J.E., Aljuboori, Z., Han, I., Abd-El-Barr, M., Lee, H.J., Sidman, R.L., Snyder, E.Y., Viapiano, M.S., Kim, S.U., Chi, J.H., Teng, Y.D., 2016. Targeted Treatment of Experimental Spinal Cord Glioma With Dual Gene-Engineered Human Neural Stem Cells. *Neurosurgery* 79, 481–491.
- Ropper, A.E., Thakor, D.K., Han, I., Yu, D., Zeng, X., Anderson, J.E., Aljuboori, Z., Kim, S.W., Wang, H., Sidman, R.L., Zafonte, R.D., Teng, Y.D., 2017. Defining recovery neurobiology of injured spinal cord by synthetic matrix-assisted hMSC implantation. *Proc. Natl. Acad. Sci. U. S. A.* 114, E820–E829.
- Ryan, K.M., Phillips, A.C., Vousden, K.H., 2001. Regulation and function of the p53 tumor suppressor protein. *Curr. Opin. Cell Biol.* 13, 332–337.
- Samaha, H., El Naggar, S., Ahmed, N., 2015. Armed hunter killers: discerning the role of adoptive T-cell transfer for glioblastoma. *Immunotherapy* 7, 481–485.
- Sampson, F.C., Hayward, A., Evans, G., Morton, R., Collett, B., 2002. Functional benefits and cost/benefit analysis of continuous intrathecal baclofen infusion for the management of severe spasticity. *J. Neurosurg.* 96, 1052–1057.
- Sampson, J.H., Heimberger, A.B., Archer, G.E., Aldape, K.D., Friedman, A.H., Friedman, H.S., Gilbert, M.R., Herndon 2nd, J.E., McLendon, R.E., Mitchell, D.A., Reardon, D.A., Sawaya, R., Schmittling, R.J., Shi, W., Vredenburgh, J.J., Bigner, D.D., 2010. Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma. *J. Clin. Oncol.* 28, 4722–4729.
- Santi, M., Mena, H., Wong, K., Koeller, K., Olsen, C., Rushing, E.J., 2003. Spinal cord malignant astrocytomas. Clinicopathologic features in 36 cases. *Cancer* 98, 554–561.
- Schellinger, K.A., Propp, J.M., Villano, J.L., McCarthy, B.J., 2008. Descriptive epidemiology of primary spinal cord tumors. *J. Neuro-Oncol.* 87, 173–179.
- Schindler, G., Capper, D., Meyer, J., Janzarik, W., Omran, H., Herold-Mende, C., Schmieider, K., Wesseling, P., Mawrin, C., Hasselblatt, M., Louis, D.N., Korshunov, A., Pfister, S., Hartmann, C., Paulus, W., Reifenberger, G., von Deimling, A., 2011. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol.* 121, 397–405.
- Schmidt, N.O., Przylecki, W., Yang, W., Ziu, M., Teng, Y.D., Kim, S.U., Black, P.M., Aboody, K.S., Carroll, R.S., 2005. Brain tumor tropism of transplanted human neural stem cells is induced by vascular endothelial growth factor. *Neoplasia* 7, 623–629.
- Schwartzentruber, J., Korshunov, A., Liu, X.Y., Jones, D.T., Pfaff, E., Jacob, K., Sturm, D., Fontebasso, A.M., Quang, D.A., Tonjes, M., Hovestadt, V., Albrecht, S., Kool, M., Nantel, A., Konermann, C., Lindroth, A., Jager, N., Rausch, T., Ryzhova, M., Korbel, J.O., Hielscher, T., Hauser, P., Garami, M., Klekner, A., Bognar, L., Ebinger, M., Schuhmann, M.U., Scheurlen, W., Pekrun, A., Fruhwald, M.C., Roggendorf, W., Kramm, C., Durken, M., Atkinson, J., Lepage, P., Montpetit, A., Zakrzewska, M., Zakrzewski, K., Liberski, P.P., Dong, Z., Siegel, P., Kulozik, A.E., Zapatka, M., Guha, A., Malkin, D., Felsberg, J., Reifenberger, G., von Deimling, A., Ichimura, K., Collins, V.P., Witt, H., Milde, T., Witt, O., Zhang, C., Castelo-Branco, P., Lichter, P., Faury, D., Tabori, U., Plass, C., Majewski, J., Pfister, S.M., Jabado, N., 2012. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature* 482, 226–231.
- Segura, M.F., Hanniford, D., Menendez, S., Reavie, L., Zou, X., Alvarez-Diaz, S., Zakrzewski, J., Blochin, E., Rose, A., Bogunovic, D., 2009. Aberrant miR-182 expression promotes melanoma metastasis by repressing FOXO3 and microphthalmia-associated transcription factor. *Proc. Natl. Acad. Sci.* 106, 1814–1819.
- Shankar, G.M., Francis, J.M., Rinne, M.L., Ramkissoon, S.H., Huang, F.W., Venteicher, A.S., Akama-Garren, E.H., Kang, Y.J., Lelic, N., Kim, J.C., Brown, L.E., Charbonneau, S.K., Golby, A.J., Sekhar Pedamallu, C., Hoang, M.P., Sullivan, J., Cherniack, A.D., Garraway, L.A., Stember-Rachamimov, A., Reardon, D.A., Wen, P.Y., Brastianos, P.K., Curry, W.T., Barker 2nd, F.G., Hahn, W.C., Nahed, B.V., Ligon, K.L., Louis, D.N., Cahill, D.P., Meyerson, M., 2015. Rapid Intraoperative Molecular Characterization of Glioma. *JAMA Oncol* 1, 662–667.
- Shankar, G.M., Lelic, N., Gill, C.M., Thorne, A.R., Van Hummelen, P., Wisoff, J.H., Loeffler, J.S., Brastianos, P.K., Shin, J.H., Borges, L.F., Butler, W.E., Zagzag, D., Brody, R.I., Duhaime, A.C., Taylor, M.D., Hawkins, C.E., Louis, D.N., Cahill, D.P., Curry, W.T., Meyerson, M., 2016. BRAF alteration status and the histone H3F3A gene K27M mutation segregate spinal cord astrocytoma histology. *Acta Neuropathol.* 131, 147–150.
- Shervington, A., Patel, R., Lu, C., Cruickshanks, N., Lea, R., Roberts, G., Dawson, T., Shervington, L., 2007. Telomerase subunits expression variation between biopsy samples and cell lines derived from malignant glioma. *Brain Res.* 1134, 45–52.
- Simon, M., Koster, G., Menon, A.G., Schramm, J., 1999. Functional evidence for a role of combined CDKN2A (p16-p14(ARF))/CDKN2B (p15) gene inactivation in malignant gliomas. *Acta Neuropathol.* 98, 444–452.
- Smith, J.S., Tachibana, I., Passe, S.M., Huntley, B.K., Borell, T.J., Iturria, N., O'Fallon, J.R., Schaefer, P.L., Scheithauer, B.W., James, C.D., Buckner, J.C., Jenkins, R.B., 2001. PTEN Mutation, EGFR Amplification, and Outcome in Patients With Anaplastic Astrocytoma and Glioblastoma Multiforme. *JNCI: Journal of the National Cancer Institute* 93, 1246–1256.
- Snyder, E.Y., Teng, Y.D., 2012. Stem cells and spinal cord repair. *N. Engl. J. Med.* 366, 1940–1942.
- Solomon, D.A., Wood, M.D., Tihan, T., Bollen, A.W., Gupta, N., Phillips, J.J., Perry, A., 2016. Diffuse Midline Gliomas with Histone H3-K27M Mutation: A Series of 47 Cases Assessing the Spectrum of Morphologic Variation and Associated Genetic Alterations. *Brain Pathol.* 26, 569–580.
- Squatrito, M., Brennan, C.W., Helmy, K., Huse, J.T., Petri, J.H., Holland, E.C., 2010. Loss of ATM/Chk2/p53 Pathway Components Accelerates Tumor Development and Contributes to Radiation Resistance in Gliomas. *Cancer Cell* 18, 619–629.
- Stupp, R., van den Bent, M.J., Hegi, M.E., 2005. Optimal role of temozolomide in the treatment of malignant gliomas. *Curr. Neurol. Neurosci. Rep.* 5, 198–206.
- Sturm, D., Witt, H., Hovestadt, V., Khuong-Quang, D.A., Jones, D.T., Konermann, C., Pfaff, E., Tonjes, M., Sill, M., Bender, S., Kool, M., Zapatka, M., Becker, N., Zucknick, M., Hielscher, T., Liu, X.Y., Fontebasso, A.M., Ryzhova, M., Albrecht, S., Jacob, K., Wolter, M., Ebinger, M., Schuhmann, M.U., van Meter, T., Fruhwald, M.C., Hauch, H., Pekrun, A., Radlwimmer, B., Niehues, T., von Komorowski, G., Durken, M., Kulozik, A.E., Madden, J., Donson, A., Foreman, N.K., Drissi, R., Fouladi, M., Scheurlen, W., von Deimling, A., Monoranu, C., Roggendorf, W., Herold-Mende, C., Unterberg, A., Kramm, C.M., Felsberg, J., Hartmann, C., Wiestler, B., Wick, W., Milde, T., Witt, O., Lindroth, A.M., Schwartzentruber, J., Faury, D., Fleming, A., Zakrzewska, M., Liberski, P.P., Zakrzewski, K., Hauser, P., Garami, M., Klekner, A., Bognar, L., Morikssy, S., Cavalli, F., Taylor, M.D., van Sluis, P., Koster, J., Versteeg, R., Volckmann, R., Mikkelson, T., Aldape, K., Reifenberger, G., Collins, V.P., Majewski, J., Korshunov, A., Lichter, P., Plass, C., Jabado, N., Pfister, S.M., 2012. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. *Cancer Cell* 22, 425–437.
- Takata, M., Sasaki, M.S., Sonoda, E., Morrison, C., Hashimoto, M., Utsumi, H., Yamaguchi-Iwai, Y., Shinohara, A., Takeda, S., 1998. Homologous recombination and non-homologous end-joining pathways of DNA double-strand break repair have overlapping roles in the maintenance of chromosomal integrity in vertebrate cells. *EMBO J.* 17, 5497–5508.
- Tanic, N., Milovanovic, Z., Tanic, N., Dzodic, R., Juranic, Z., Susnjak, S., Plesinac-Karapandzic, V., Tatic, S., Dramicanin, T., Davidovic, R., Dimitrijevic, B., 2012. The impact of PTEN tumor suppressor gene on acquiring resistance to tamoxifen treatment in breast cancer patients. *Cancer Biology & Therapy* 13, 1165–1174.
- Teasell, R.W., Arnold, J.M., Krassioukov, A., Delaney, G.A., 2000. Cardiovascular consequences of loss of supraspinal control of the sympathetic nervous system after spinal cord injury. *Arch. Phys. Med. Rehabil.* 81, 506–516.
- Teng, Y.D., Wrathall, J.R., 1996. Evaluation of cardiorespiratory parameters in rats after spinal cord trauma and treatment with NBQX, an antagonist of excitatory amino acid receptors. *Neurosci. Lett.* 209, 5–8.
- Teng, Y.D., Mocchetti, I., Taveira-DaSilva, A.M., Gillis, R.A., Wrathall, J.R., 1999. Basic fibroblast growth factor increases long-term survival of spinal motor neurons and improves respiratory function after experimental spinal cord injury. *J. Neurosci.* 19, 7037–7047.
- Teng, Y.D., Lavik, E.B., Qu, X., Park, K.I., Ourednik, J., Zurakowski, D., Langer, R., Snyder, E.Y., 2002. Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. *Proc. Natl. Acad. Sci. U. S. A.* 99, 3024–3029.
- Teng, Y.D., Yu, D., Ropper, A.E., Li, J., Kabatas, S., Wakeman, D.R., Wang, J., Sullivan, M.P., Redmond Jr., D.E., Langer, R., Snyder, E.Y., Sidman, R.L., 2011. Functional multipotency of stem cells: a conceptual review of neurotrophic factor-based evidence and its role in translational research. *Curr. Neuropharmacol.* 9, 574–585.
- Teng, Y.D., Benn, S.C., Kalkanis, S.N., Shefner, J.M., Onario, R.C., Cheng, B., Lachyankar, M.B., Marconi, M., Li, J., Yu, D., Han, I., Maragakis, N.J., Llado, J., Erkmann, K., Redmond Jr., D.E., Sidman, R.L., Przedborski, S., Rothstein, J.D., Brown Jr., R.H., Snyder, E.Y., 2012. Multimodal actions of neural stem cells in a mouse model of ALS: a meta-analysis. *Sci. Transl. Med.* 4, 165ra164.
- Teng, Y.D., Snyder, E.Y., Zeng, X., Anderson, J.E., Han, I.B., 2017. Multimodal Neural Stem Cell Research Protocols for Experimental Spinal Cord Injuries. In: Srivastava, A.K., Snyder, E.Y., Teng, Y.D. (Eds.), *Stem Cell Technologies in Neuroscience*. Springer, San Diego, CA.
- Teng, Y.D., Wang, L., Kabatas, S., Ulrich, H., Zafonte, R., 2018. Cancer stem cells or tumor survival cells. *Stem Cell Dev In press*.
- Toktas, Z.O., Yilmaz, B., Eksi, M.S., Wang, L., Akakin, A., Yener, Y., Konakci, M., Ayan, E., Kilic, T., Konya, D., Teng, Y.D., 2018. An iMRI-assisted Case of Cervical Intramedullary Diffuse Glioma Resection. *Cancer Manag. Res In press*.
- Tong, Y.Q., Liu, B., Zheng, H.-Y., Gu, J., Liu, H., Li, F., Tan, B.H., Hartman, M., Song, C., Li, Y., 2015. MiR-215, an activator of the CTNBP1/β-catenin pathway, is a marker of poor prognosis in human glioma. *Oncotarget* 6, 25024–25033.
- Turcan, S., Rohle, D., Goenka, A., Walsh, L.A., Fang, F., Yilmaz, E., Campos, C., Fabius, A.W.M., Lu, C., Ward, P.S., Thompson, C.B., Kaufman, G., Guryanova, O., Levine, R., Heguy, A., Viale, A., Morris, L.G.T., Huse, J.T., Mellinghoff, I.K., Chan, T.A., 2012. IDH1 mutation is sufficient to establish the glioma hypermethylation phenotype. *Nature* 483, 479–483.
- Tyler, B.M., Hdeib, A., Caplan, J., Legnani, F.G., Fowers, K.D., Brem, H., Jallo, G., Pradilla, G., 2012. Delayed onset of paresis in rats with experimental intramedullary spinal cord gliosarcoma following intratumoral administration of the paclitaxel delivery system OncoGel. *J. Neurosurg Spine* 16, 93–101.
- Verla, T., Fridley, J.S., Khan, A.B., Mayer, R.R., Omeis, I., 2016. Neuromonitoring for Intramedullary Spinal Cord Tumor Surgery. *World Neurosurg* 95, 108–116.
- von Deimling, A., Korshunov, A., Hartmann, C., 2011. The next generation of glioma biomarkers: MGMT methylation, BRAF fusions and IDH1 mutations. *Brain Pathol.* 21, 74–87.
- Wainwright, D.A., Chang, A.L., Dey, M., Balyasnikova, I.V., Kim, C.K., Tobias, A., Cheng, Y., Kim, J.W., Qiao, J., Zhang, L., Han, Y., Lesniak, M.S., 2014. Durable therapeutic efficacy utilizing combinatorial blockade against IDO, CTLA-4, and PD-L1 in mice with brain tumors. *Clin. Cancer Res.* 20, 5290–5301.
- Wakefield, A., Pignata, A., Ghazi, A., Ashoori, A., Hegde, M., Landi, D., Gray, T., Scheurer, M.E., Chintagumpala, M., Adesina, A., Gottschalk, S., Hicks, J., Powell, S.Z., Ahmed, N., 2015. Is CMV a target in pediatric glioblastoma? Expression of CMV proteins, pp65 and IE1-72 and CMV nucleic acids in a cohort of pediatric glioblastoma

- patients. *J. Neuro-Oncol.* 125, 307–315.
- Walboomers, J.M., Jacobs, M.V., Manos, M.M., Bosch, F.X., Kummer, J.A., Shah, K.V., Snijders, P.J., Peto, J., Meijer, C.J., Munoz, N., 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J. Pathol.* 189, 12–19.
- Wang, S., Lu, S., Geng, S., Ma, S., Liang, Z., Jiao, B., 2013. Expression and clinical significance of microRNA-326 in human glioma miR-326 expression in glioma. *Med. Oncol.* 30, 373.
- Wiedenheft, B., Sternberg, S.H., Doudna, J.A., 2012. RNA-guided genetic silencing systems in bacteria and archaea. *Nature* 482, 331–338.
- Wrensch, M., Jenkins, R.B., Chang, J.S., Yeh, R.-F., Xiao, Y., Decker, P.A., Ballman, K.V., Berger, M., Buckner, J.C., Chang, S., Giannini, C., Halder, C., Kollmeyer, T.M., Kosel, M.L., LaChance, D.H., McCoy, L., O'Neill, B.P., Patoka, J., Pico, A.R., Prados, M., Quesenberry, C., Rice, T., Rynearson, A.L., Smirnov, I., Tihan, T., Wiemels, J., Yang, P., Wiencke, J.K., 2009a. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nat. Genet.* 41, 905.
- Wrensch, M., Jenkins, R.B., Chang, J.S., Yeh, R.F., Xiao, Y., Ballman, K.V., Berger, M., Buckner, J.C., Chang, S., Decker, P.A., Giannini, C., Halder, C., Kollmeyer, T.M., Kosel, M.L., LaChance, D.H., McCoy, L., O'Neill, B., Patoka, J., Pico, A.R., Prados, M., Quesenberry, C., Rice, T., Rynearson, A., Smirnov, I., Tihan, T., Wiemels, J., Yang, P., Wiencke, J.K., 2009b. Variants in the CDKN2B and RTEL1 regions are associated with high grade glioma susceptibility. *Nat. Genet.* 41, 905–908.
- Wu, G., Broniscer, A., McEachron, T.A., Lu, C., Paugh, B.S., Beckford, J., Qu, C., Ding, L., Huether, R., Parker, M., Zhang, J., Gajjar, A., Dyer, M.A., Mullighan, C.G., Gilbertson, R.J., Mardis, E.R., Wilson, R.K., Downing, J.R., Ellison, D.W., Zhang, J., Baker, S.J., 2012. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat. Genet.* 44, 251–253.
- Yang, H., Ye, D., Guan, K.L., Xiong, Y., 2012. IDH1 and IDH2 mutations in tumorigenesis: mechanistic insights and clinical perspectives. *Clin. Cancer Res.* 18, 5562–5571.
- Yang, H.W., Chung, M., Kudo, T., Meyer, T., 2017. Competing memories of mitogen and p53 signalling control cell-cycle entry. *Nature* 549, 404–408.
- Yin, Y., Shen, W.H., 2008. PTEN: a new guardian of the genome. *Oncogene* 27, 5443.
- Yu, D., Thakor, D.K., Han, I., Ropper, A.E., Haragopal, H., Sidman, R.L., Zafonte, R., Schachter, S.C., Teng, Y.D., 2013. Alleviation of chronic pain following rat spinal cord compression injury with multimodal actions of huperzine A. *Proc. Natl. Acad. Sci. U. S. A.* 110, E746–E755.
- Zadnik, P.L., Gokaslan, Z.L., Burger, P.C., Bettgowda, C., 2013. Spinal cord tumours: advances in genetics and their implications for treatment. *Nat. Rev. Neurol.* 9, 257–266.
- Zeng, X., Han, I., Abd-El-Barr, M., Aljuboori, Z., Anderson, J.E., Chi, J.H., Zafonte, R.D., Teng, Y.D., 2016. The Effects of Thermal Preconditioning on Oncogenic and Intraspinal Cord Growth Features of Human Glioma Cells. *Cell Transplant.* 25, 2099–2109.
- Zhang, W., Zhang, J., Hoadley, K., Kushwaha, D., Ramakrishnan, V., Li, S., Kang, C., You, Y., Jiang, C., Song, S.W., Jiang, T., Chen, C.C., 2012. miR-181d: a predictive glioblastoma biomarker that downregulates MGMT expression. *Neuro-Oncology* 14, 712–719.
- Zhao, S., Lin, Y., Xu, W., Jiang, W., Zha, Z., Wang, P., Yu, W., Li, Z., Gong, L., Peng, Y., Ding, J., Lei, Q., Guan, K.L., Xiong, Y., 2009. Glioma-Derived Mutations in IDH1 Dominantly Inhibit IDH1 Catalytic Activity and Induce HIF-1 α . *Science* 324, 261–265.
- Zhao, S., Yang, G., Mu, Y., Han, D., Shi, C., Chen, X., Deng, Y., Zhang, D., Wang, L., Liu, Y., Hou, X., Wang, C., Wu, J., Liu, H., Wang, L., Zhang, G., Qi, J., Fang, X., Shi, C., Ai, J., 2013. MiR-106a is an independent prognostic marker in patients with glioblastoma. *Neuro-Oncology* 15, 707–717.