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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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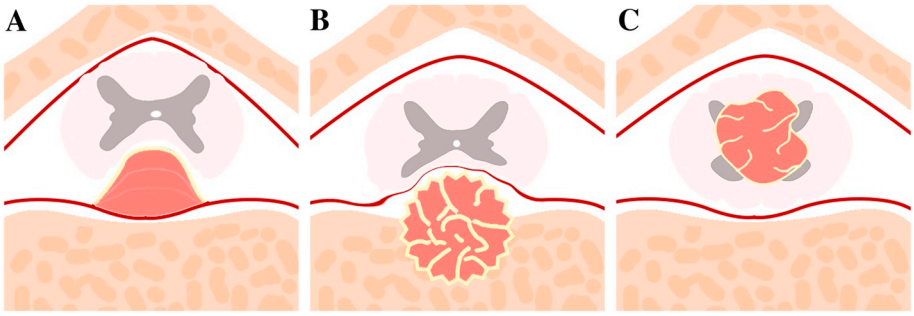

Fig. 1. The three general pathological types of spinal tumors.
(A) Extradural neoplasms: The majority of neoplastic lesions (~ 60%) grow extradurally and originate from the vertebrae, for which metastasis is the most frequent cause. (B) Extramedullary neoplasms: Intradural tumors are relatively rare 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., infiltrative 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

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