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Mini Review

Medulloblastoma: From Origin to Treatment

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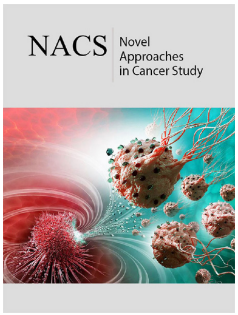

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Abstract

Medulloblastoma is the most frequent childhood brain tumor. Medulloblastoma affects the cerebellum, the brain region that regulates motor coordination and is also involved in certain cognitive functions. Medulloblastoma is a heterogeneous tumor, and recent advances in high-throughput genomic techniques have allowed medulloblastoma to be classified into four molecularly distinct subgroups: the SHH-group, WNT-group, group 3, and group 4 medulloblastoma. Different medulloblastoma subgroups are characterized by distinct molecular alterations, are believed to originate from distinct types of neural progenitors, and have different clinical outcomes. WNT and SHH groups are relatively well understood and are named so because the WNT and SHH signaling pathways play a key role in their development. In contrast, molecular alterations and developmental mechanisms of group 3 and 4 medulloblastoma remain largely unknown. Although the survival of medulloblastoma patients has improved over the last 30 years, reaching the 5-year survival rate of 60-80%, treatment of this type of tumor is still associated with severe side effects. A deeper understanding of medulloblastoma biology and developing new pathway-specific therapies is urgently required for better treatment of medulloblastoma patients.

Keywords: Medulloblastoma; Cerebellum; Development; Medulloblastoma subgroups; Medulloblastoma pathways

Introduction

Medulloblastoma is a brain tumor, which is most frequently diagnosed in children [1,2]. The term "medulloblastoma" was introduced by Drs. Cushing and Bailey in 1925 to describe childhood tumors located in the posterior fossa, a cerebrospinal fluid- filled space located at the back of the skull [3]. During the following decades, it was determined that most medulloblastoma cases originate in the cerebellum, the brain region that is responsible for motor-coordination and certain higher order cognitive functions. Traditionally, medulloblastoma was classified based on histology. In 2016, a new classification of medulloblastoma, which better reflects its pathology and prognosis, was introduced. This classification is largely based on molecular alterations observed in medulloblastoma tumors and subdivides all medulloblastoma cases into four groups: the SHH group, WNT group, and groups 3 and 4 [4].

Growing evidence indicates that medulloblastoma arises when genetic and epigenetic alterations compromise the normal cerebellar developmental program, in particular the proliferation and differentiation of cerebellar progenitors and stem cells [5]. It is believed that each group of medulloblastoma arises from a distinct type of cerebellar progenitors and is driven by specific genetic and epigenetic alterations [6]. While well established for some medulloblastoma groups (such as for the SHH group and to a lesser degree for the WNT group), the developmental origin and molecular mechanisms for other medulloblastoma types are poorly understood [7-9].

Despite the advancement of medulloblastoma treatment protocols, the 5-year survival rate of medulloblastoma patients does not typically exceed 70%, and medulloblastoma treatment remains to be associated with significant side effects [3]. A better understanding of the mechanisms that drive medulloblastoma formation is clearly important for the development of more efficient medulloblastoma treatment strategies. In this review, we will discuss the cellular and molecular mechanisms that regulate normal cerebellar development and how their disruption leads to the development of specific types of medulloblastoma.

Cerebellar development

During development, the cerebellar anlage arises from the alar plate (dorsal region) of rhombomere 1 in the anterior hindbrain [10]. Because of the limited availability of human embryonic tissue, most of our knowledge about cerebellar neurogenesis came from the analysis of model organisms, particularly mice. It is believed, however, that cerebellar development is largely conserved between humans and mice, and, thus, key developmental mechanisms identified in mice are also applicable to the human cerebellum [11,12].

Once established during early embryogenesis, the cerebellar anlage harbors two germinal zones (progenitor domains): the cerebellar ventricular zone and cerebellar rhombic lip (Figure 1). The cerebellar ventricular zone produces GABAergic cerebellar neurons, including Purkinje neurons [13]. Purkinje neurons exit the ventricular zone largely as post-mitotic cells and migrate radially from the site of their origin. Another cellular population that arises from the cerebellar ventricular zone are astroglial like progenitors. After exiting the cerebellar ventricular zone, astroglial-like progenitors populate cerebellar parenchyma and later cerebellar white matter, where they proliferate and eventually produce GABAergic interneurons, cerebellar glia, and, likely, also give rise to stem cells that continue populating the cerebellar white matter. The cerebellar rhombic lip is the initial place of origin of all glutamatergic (excitatory) neurons of the cerebellum, such as granule cells and neurons of cerebellar nuclei [14]. Glutamatergic cerebellar neurons exit the rhombic lip during early embryonic development and tangentially migrate to the nuclear transitory zone before forming deep cerebellar nuclei. Then, the rhombic lip begins producing granule cell precursors that generate the external granule layer (EGL), which is a secondary germinal zone in the late embryonic and early postnatal cerebellum (Figure 1) [14,15]. Granule cells are the most abundant neurons in the entire brain and account for 80% of all neurons in humans and 60% of neurons in mice. Thus, dramatic expansion of granule precursors in the EGL due to proliferation is necessary to produce enough mature granule neurons to establish proper cerebellar circuits [12].

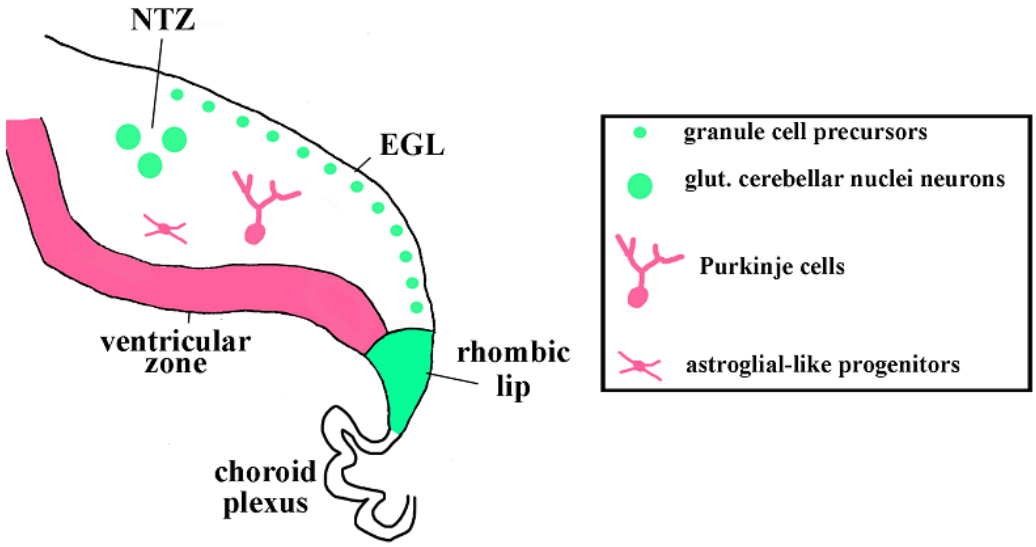

Figure 1: Key cell types and their origin in the developing cerebellum.

The sagittal section of the developing cerebellum is shown. The external granule cell layer (EGL) and nuclear transitory zone (NTZ) are labeled. Glutamatergic cerebellar neurons (cerebellar nuclei neurons and granule precursors) originate from the rhombic lip (green), which is located adjacent to the choroid plexus. GABAergic cerebellar cell types (Purkinje cells and astroglial-like progenitors that produce molecular layer interneurons) originate from the ventricular zone (pink).

During late embryogenesis (around postnatal days 1-3 in mice), Purkinje cells begin forming a monolayer below the EGL. They secrete sonic hedgehog (SHH) protein, a potent mitogen for granule cell precursors, thus, regulating the proliferation and expansion of granule cells (Figure 2) [16-19]. After exiting the cell cycle and beginning differentiation, granule cells migrate inward along Bergmann glial fibers. This leads to the disappearance of the EGL and the formation of the internal granule cell layer (IGL) beneath

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the Purkinje cell layer. In mice, the EGL disappears by postnatal day 16, but in humans the EGL persists much longer, and is still detected one year after birth [20].

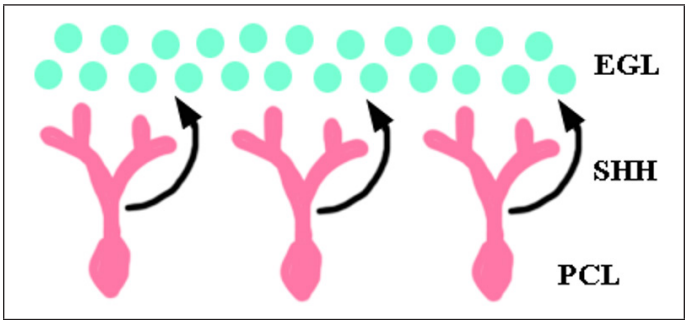

Figure 2: Purkinje cells secrete SHH to promote the proliferation of progenitors in the EGL.

Purkinje cells are pink, granule cell precursors are green. PCL - Purkinje cell layer. Arrows indicate SHH protein secreted by Purkinje cells that reaches granule cell precursors.

More than a hundred genes are known to regulate cerebellar development. Since the genetic regulation of cerebellar development has been the focus of several recent reviews [11,21,22], this topic will only be briefly touched in this paper. Probably the most well-known transcription factors that regulate cerebellar development are Atoh1, Pax6 and Zic1. They are expressed in granule cell precursors in the EGL and regulate the migration, proliferation and survival of these cells [23-25]. N-Myc, C-Myc, and Gli also regulate the proliferation of cerebellar progenitors, particular granule precursors in the EGL [26,27]. Wnt signaling, a well-known mitogen for many types of cells, promotes the progenitor expansion in the ventricular zone, cerebellar parenchyma and white matter. Interestingly, Wnts do not promote expansion of granule cell precursors, highlighting the difference in the molecular networks that operate in distinct progenitor domains [28].

Medulloblastoma: Epidemiology, developmental origin, and molecular pathways

Most medulloblastoma cases are diagnosed in children younger than nine years old, although medulloblastoma can also develop in adults, typically those younger than 40 years. Most medulloblastoma cases are sporadic, and fewer than 5% are associated with familial cancer predisposition syndromes. Boys have a slightly higher frequency of medulloblastoma than girls, and no significant difference in medulloblastoma incidence was reported between different races and ethnic groups [1-3].

In contrast to many other human cancers, no clear association with non-genetic risk factors, such as environmental exposures, has been identified for medulloblastoma. Similar to other tumors, however, medulloblastoma arises as the result of the accumulation of oncogenic mutations and epigenetic changes in neural progenitors or stem cells [5]. The genetic and epigenetic changes found in different cases of medulloblastoma, as well as their cells of origin, significantly affect tumor behavior and prognosis, and allow the classification of medulloblastoma into four major subgroups. These four groups are discussed below, including their cells of origin and the most common mutations.

SHH group

Approximately 25% of medulloblastoma cases belong to the SHH subgroup and are characterized by an intermediate prognosis (60-80% survival rate) [6]. Medulloblastomas of this subgroup arise from granule cell precursors in the EGL because of an overactivation of the SHH signaling pathway, an important regulator of normal granule cell development [7,8]. Different genetic events affecting the SHH pathway have been described in SHH medulloblastomas. These include mutations inactivating negative regulators of the SHH Pathway, including PTCH1 and SUFU, and mutations activating positive regulators or downstream effectors of the SHH pathway such as SMO, GLI1, GLI2, YAP1 and MYCN [29,30]. Mutations of tumor suppressor p53 have been reported as well [31].

WNT group

Approximately 10% of medulloblastomas belong to this group. It is characterized by an excellent (more than 95%) survival rate [6]. Surprisingly, at least some tumors of this group arise from progenitors outside the cerebellum, in the lower rhombic lip – the most dorsal region of the brainstem [32,33]. The vast majority (up to 90%) of WNT medulloblastomas possess mutations activating the CTNB1 gene that encodes beta-catenin, the downstream mediator of the WNT signaling pathway [30]. Activated beta-catenin enters the nucleus and activates the expression of its downstream genes, many of which are positive regulators of the cell cycle, and thus, promote proliferation of medulloblastoma cells. Loss-of-function mutations of APC, an inhibitor of the WNT signaling pathway, were discovered in the WNT group of medulloblastoma as well [34].

Group 3

This is the most aggressive type of medulloblastoma (survival rate is less than 60%). Approximately 25% of medulloblastomas belong to this group [6]. Group 3 medulloblastomas are characterized by the amplification and overexpression of MYCN but not other SHH-related genes [31]. Alterations in the NOTCH signaling pathway, transcription factor OTX2, and multiple proteins involved in transcription and translation have also been reported in this type of medulloblastoma [35]. The cellular origin of group 3 medulloblastoma is poorly understood, but it is believed that this type of medulloblastoma arises from ventricular zone progenitors or other progenitors in the embryonic or neonatal cerebellum [59].

Group 4

This is the most common but least understood group of medulloblastoma. It is characterized by an intermediate prognosis. Mutations and the misregulation of expression of multiple genes have been described in group 4 medulloblastoma, but none of the genes are mutated in more than 10% of cases [6,30]. Recent gene expression studies suggest that Group 4 medulloblastomas originate from glutamatergic deep cerebellar nuclei progenitors, possibly those located in the early cerebellar rhombic lip [9].

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Medulloblastoma treatment

Medulloblastoma treatment involves a combination of radiation therapy, surgery, and chemotherapy [36]. Conventional medulloblastoma treatment results in ~70% of the overall five-year survival rate but frequently leads to severe life-long side effects, which include the disruption of the endocrine system, neurocognitive impairment, and the formation of secondary tumors [37-40]. Work on improving medulloblastoma treatment involves several areas, including optimization of surgery, radiotherapy optimization, and the development of targeted therapies that focus on the molecular pathways that drive medulloblastoma development. Several drugs targeting specific molecular pathways are currently in clinical trial. For example, a SMO inhibitor known as Vismodegib may improve the treatment of SHH subgroup medulloblastoma [36,41]. Unfortunately, little progress has been made in the development of targeted therapy for the most aggressive or most common medulloblastoma groups (groups 3 and 4). No direct suitable inhibitor for MYCN to target group 3 medulloblastoma and no predominant molecular target for group 4 medulloblastoma have been identified yet.

Another attractive option for medulloblastoma treatment is targeting tumor-initiating stem cells. Although radiation and chemotherapy are effective against rapidly proliferating tumor cells, they are not very effective against slowly proliferating medulloblastoma-initiating stem cells, which may be largely responsible for tumor relapse and dissemination [5,42]. The development of agents against medulloblastoma-initiating stem cells is prevented by a poor understanding of the biological nature of these cells.

Conclusion

During the last two decades, significant progress has been made in our understanding of the molecular and cellular mechanisms that drive medulloblastoma formation, in particular the SHH and WNT groups of medulloblastomas. In contrast, the most aggressive and/or most common medulloblastoma, groups 3 and 4, remain poorly understood. A better understanding of medulloblastoma biology is expected to help develop more efficient treatment strategies that will improve patients' survival rates and reduce side effects.

Competing Interests

The authors have declared that no competing interest exists.

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