Bull Cancer 2015; □□: □□□

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Review

Insights into cerebellar development and medulloblastoma

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Received 9 November 2015
Accepted 9 November 2015
Available online:

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Keywords
Cerebellar development
Medulloblastoma
Neuronal progenitors
Signaling pathways
Patient-derived xenografts
Mouse models

Summary

Cerebellar development is an extensive process that begins during early embryonic stages and persists more than one year after birth in human. Therefore, the cerebellum is susceptible to acquire various developmental abnormalities leading to numerous diseases such as medulloblastoma, the most common pediatric malignant brain tumor. One third of the patients with medulloblastoma are incurable and survivors have a poor quality of life due to the aggressiveness of the broad-spectrum treatments. Within the past few years, it has been highlighted that medulloblastoma is a heterogeneous disease that is divided in four molecular subgroups. This recent advance in the field, combined with the development of associated preclinical models for each subgroup, should enable, in the future, the discovery and use of targeted therapy in clinical treatments for each subtype of medulloblastoma. In this review, we first aim to show how deregulation of cerebellar development can lead to medulloblastoma formation and then to present the advances in the molecular subgrouping of medulloblastoma and the associated preclinical models.

Mots clés
Développement cérébelleux
Médulloblastome
Progéniteurs neuronaux
Voies de signalisation
Xénogreffes dérivées de patients
Modèles murins

Résumé

Dérégulation du développement cérébelleux et médulloblastomes

Le développement du cervelet est un processus complexe qui se déroule à partir des stades embryonnaires précoces jusqu'à plus d'un an après la naissance chez l'homme. Par conséquent, le cervelet est susceptible d'acquérir diverses anomalies au cours du développement pouvant être à l'origine de pathologies telles que le médulloblastome, la tumeur cérébrale maligne la plus fréquente chez l'enfant. Un tiers des patients atteints d'un médulloblastome est incurable et les survivants souffrent de séquelles en raison de l'agressivité des traitements. Au cours des dernières années, il a été démontré que le médulloblastome est une maladie hétérogène divisée en quatre sous-groupes. Cette découverte, combinée à l'élaboration de modèles précliniques associés à chaque sous-groupe, devrait permettre, à l'avenir, le développement et

http://dx.doi.org/10.1016/j.bulcan.2015.11.002

To cite this article: Bihannic L, Ayrault O. Insights into cerebellar development and medulloblastoma. Bull Cancer (2015), http://dx.doi.org/10.1016/j.bulcan.2015.11.002

l'utilisation de thérapies ciblées pour chaque sous-type de médulloblastome. Dans cette revue, nous allons décrire comment la dérégulation du développement du cervelet peut conduire à la formation de médulloblastome, puis présenter les avancées dans la classification moléculaire des sous-groupes et les modèles pré-cliniques associés.

Introduction

The central nervous system (CNS) is composed of the brain and the spinal cord. The brain, which is embedded within the skull, is divided into three major components: the brainstem, the cerebrum and the cerebellum (*figure 1*A). Although the cerebellum represents only 10% of the brain volume, it bears more than half of the total amount of neurons. Cerebellum operates as a coordination center by controlling smooth and skillful movements using sensory inputs from the periphery. It is also involved in cognitive functions, including feed-forward sensory-motor learning, speech and spatial memory. Cerebellar development is tightly regulated, and dysfunction in this process could lead to cancer, as well as, neurological disorders. In this review we will describe how deregulation of cerebellar development can lead to the formation of the most malignant pediatric brain tumor, medulloblastoma.

Cerebellar morphology

The mediolateral axis of the cerebellum is divided into two regions: the vermis (medial region), and the hemispheres (lateral regions) (*figure 1*A). The cerebellum is a lobular organ and its vermis is divided into ten primary lobules (I-X) in mammals that can be further divided into sublobules (*figure 1*B).

The cerebellum contains several types of neurons that are classified in two major categories: excitatory and inhibitory neurons. The excitatory neurons, or glutamatergic neurons, are composed of cerebellar granule cells, unipolar brush cells and large neurons in the deep cerebellar nuclei. The inhibitory neurons, or GABAergic neurons, include Purkinje cells, Golgi cells, Lugaro cells, candelabrum cells, basket cells, stellate cells and small neurons in the deep nuclei. In addition to these neuronal cells, the cerebellum is composed by astrocytes including Bergmann glia and oligodendrocytes [1].

In order to form the cerebellum, these cells are organized in three cellular layers that overlay an inner core composed of white matter and three pairs of deep cerebellar nuclei. These three cellular layers are, from outside to inside: the molecular layer, the Purkinje cell layer and the granule cell layer [1] (*figure 1*C).

Cerebellar development

In human, the development of the cerebellum extends from the early embryonic phase, around week four with the development of the cerebellar primordium to more than one postnatal year. In mouse, the cerebellum originates from the dorsal rhombomere 1 of the hindbrain at embryonic day 9 (E9). By E17, four fissures divide the cerebellum into five folds. At birth, the development of the cerebellum is not finalized, and it is only at postnatal day 21 (P21) that the cerebellum becomes fully organized and mature.

The cerebellar neurons come from two distinct germinal zones: the ventricular zone and the upper rhombic lip. The ventricular zone, located at the roof of the fourth ventricle, is characterized by the expression of the proneural gene *Ptf1a* and gives rise to the GABAergic neurons, whereas the upper rhombic lip, localized at the caudal edge of the cerebellar primordium, expresses specifically the transcription factor *Atoh1* and gives rise to the glutamatergic neurons [4–6] (*figure 2*A and B). Each type of cerebellar neuron is produced at a specific time. Among the glutamatergic neurons, the granule neuron progenitors (GNPs) are produced from the upper rhombic lip starting at E12.5 and tangentially migrate from the cerebellar rhombic lip to the surface of the cerebellum to form the external granule layer (EGL).

During the postnatal stage, GNPs undergo a rapid and massive proliferation in the external granule layer starting from P2 until around P15. This massive proliferation is due principally to the soluble mitogen Sonic Hedgehog (SHH) that is released from the Purkinje cells. SHH ligand acts through the 12-pass transmembrane protein Patched1 (Ptch1) at the surface of the GNPs. In the absence of SHH, Ptch1 represses the function of the seven-pass transmembrane Smoothened (Smo) receptor by preventing its trafficking and localization at the cilia, a non-motile microtubule-based organelle required for SHH signaling in mammals (*figure 3*A). The binding of SHH on Ptch1 releases the repression of Ptch1 on Smo and allows its accumulation in the primary cilia. This will further induce the activation and nuclear translocation of the active form of the transcription factor Gli1/2, leading to the transcription of pro-proliferative genes such as *Cyclin D1*, *Cyclin D2*, *N-Myc*, *Gli1* (*figure 3*B).

The major role of SHH on GNP proliferation was highlighted using different approaches including the use a biologically active N-terminal fragment of SHH in culture or, separately, a blocking anti-SHH antibody in vivo [7–9]. More recently, conditional knockout mice for *Smo* or *Gli* as well as major components of primary cilia intraflagellar transport 88 homolog (*IFT88*) and the kinesin family member 3a (*Kif3a*) confirmed the role of SHH in GNP proliferation [10,11].