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DEVELOPMENTAL GENETICS OF THE CEREBELLUM

The cerebellum is a member of the rhombencephalon and it is ovoid structure located the posterior cranial fossa inferior to the tentorium cerebelli. In an adult, the weight of the cerebellum is about 150g. This is about 10% of the weight of the cerebral hemispheres. Like the cerebrum, the cerebellum has a superficial layer of gray matter, the cerebella cortex. Because of the presence of numerous fissures, the cerebella cortex is much more extensive than the size of this part of the brain would suggest.

The cerebellum lies behind the pons and medulla. Anteriorly the fourth ventricle intervenes between the cerebellum (behind) and the pons and medulla (in front). Part of the cavity of the ventricle extends into the cerebellum as a transverse cleft. This cleft is bounded cranially by the superior (or anterior) medullary velum, a lamina of white matter.

Some functions of the cerebellum include

* Maintenance of balance and posture
* Coordination of voluntary movement
* Motor learning
* Cognitive function

Different genes contribute to the development of the cerebellum, they include;

* Otx2: OTX2 (orthodenticle homeobox 2) is a transcription factor responsible for mediating embryogenesis in the CNS, regulating formation of the brain parenchyma, pineal gland, cerebellum, eye, and the external granule cell layer in cerebellar development, a site extremely relevant in medulloblastoma development.
* Gbx2: The Gbx2 lineage gives rise to Purkinje cells, granule neurons, and deep cerebellar neurons across these marking stages. Notably, the contribution of the Gbx2 lineage shifts as development proceeds with each marking stage producing a distinct profile of mature neurons in the adult cerebellum.
* Fgf8: A crucial role for sustained Fgf8 function is in repressing Otx2 in the hindbrain, thereby allowing the isthmus and cerebellum to form. Fgf8 is also required to maintain the borders of expression of a number of key genes involved in tectal-isthmo-cerebellum development.
* Wnt1: Wnt1 expression temporarily allocates upper rhombic lip progenitors and defines their terminal cell fate in the cerebellum.
* En1 & En2: The [engrailed genes](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/engrailed-gene) (En1and En2) are expressed in all cerebellar cell types and are critical for regulating formation of specific fissures. However, the cerebellar cell types that En1and En2 act in to control growth and/or patterning of fissures has not been determined.

the cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip. The mesencephalon and metencephalon both contribute to the developing mouse cerebellum. The patterning of these two regions depends on signals from the isthmus organizer (IO), located just caudal to their junction. Otx2 and Gbx2 are central to isthmus organizer development. Otx2 is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon; Gbx2 is expressed in the metencephalon, and its anterior boundary abuts the Otx2 boundary. Reciprocal repression maintains a sharp boundary between these domains. Otx2 and Gbx2 form part of a regulatory loop that includes Wnt1, En1 and Fgf8. Many other genes, including members of the Pax and Hox families, are also involved in patterning this region. Purkinje cells, Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium. Purkinje cells are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, purkinje cells develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including Wnt3. Various growth factors are required for purkinje cell survival, including nerve growth factor, acetylcholine, neurotrophin 4/5, brain-derived neurotrophic factor and ciliary neurotrophic factor.

The rhombic lip, located between the fourth ventricle and the metencephalic roof plate, gives rise to granule neurons. Proliferation in its germinal epithelium is governed by the Math1 gene. Rhombic lip cells migrate to the cerebellar anlage and settle on its periphery to form the external granule layer, another zone of proliferation. As the cells begin to migrate, they express markers that include RU49/Zipro1, Zic1 and Zic3. RU49/Zipro1 and Zic1 are thought to be involved in cell proliferation, which requires interaction with purkinje cells. Purkinje cells might release a diffusible factor such as sonic hedgehog (Shh), and Zic1 could control cell proliferation by indirectly regulating the Shh pathway. The final stage of granule neuron maturation occurs after precursor cell migration into the inner granule layer.

Many genes, including En1, En2, Pax2, Wnt7b, and some of the ephrins and their receptors, show characteristic patterns of spatial expression in the cerebellum, but only En2 has been studied specifically for its role in compartmentalization. In addition to the patterning genes, several other gene families, such as the heat shock proteins and proteins involved in neuronal migration, are also expressed in specific patterns. Spatial- and temporal-specific knockout strategies should yield more information about the roles of these genes in patterning the cerebellum.

GENETIC BASIS OF KNOWN CEREBELLAR DISORDERS

1. Ataxia: it is caused by progressive atrophy of the cerebellum and a clear loss of Purkinje cells.
2. Dysarthria: it can be caused by mutation of FMR1 gene or deletion of long arm of chromosome 15.
3. Nystagmus: it is caused by mutation in the FRMD7 gene

REFRENCES;

Textbook of human neuroanatomy by inderbir singh, page 131

Wikipedia

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