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**DEVELOPMENTAL GENETICS OF THE CEREBELLUM**

**ABSTRACT**

The cerebellum is a pivotal centre for the integration and processing of motor and sensory information. Its extended development into the postnatal period makes this structure vulnerable to a variety of pathologies, including neoplasia. These properties have prompted intensive investigations that reveal not only developmental mechanisms in common with other regions of the neuraxis but also unique strategies to generate neuronal diversity. How the phenotypically distinct cell types of the cerebellum emerge rests on understanding how gene expression differences arise in a spatially and temporally coordinated manner from initially homogeneous cell populations. Increasingly sophisticated fate mapping approaches, culminating in genetic-induced fate mapping, have furthered the understanding of lineage relationships between early- versus later-born cells. Tracing the developmental histories of cells in this way coupled with analysis of gene expression patterns has provided insight into the developmental genetic programmes that instruct cellular heterogeneity. A limitation to date has been the bulk analysis of cells, which blurs lineage relationships and obscures gene expression differences between cells that underpin the cellular taxonomy of the cerebellum. This work emphasises recent discoveries, focusing mainly on single-cell sequencing in mouse and parallel human studies that elucidate neural progenitor developmental trajectories with unprecedented resolution. The result is a wealth of new information about the developmental mechanisms that generate cerebellar neural diversity.

**INTRODUCTION**

The study of spontaneous neurological mouse mutants aided many initial discoveries concerning cerebellar developments. Significant advances in mouse genetics have allowed for more targeted studies using engineered gene knockouts and transgenic mice. These mice have facilitated the examination of more subtle phenotypes such as mild behavioral abnormalities and small disruptions in cerebellar circuitry. Genetics has recently enabled the identification of genes **causing human pontocerebellar hypoplasia, Joubert syndrome and Dandy-Walker malformation (DWM).** When combined with studies in mouse, a variety of molecular mechanisms, including transcriptional regulation, mitochondrial function and ciliary signaling have been implicated in homeostasis, pattering and cell proliferation during cerebellar development. Here we discuss these issues and advocate the integrated use of human and mouse systems to further explain the basis of cerebellar development.

Analysis of mouse and chick embryos reveals the cerebellum arises from the anterior hindbrain following the induction by the isthmic organiser of fate-determining gene expression domains that prefigure this structure. Organisers are groups of cells in the embryo that share the property of being able to induce a coherent set of structures in surrounding responsive tissue. Two critical determinants of regional identity, orthodenticle homeobox 2 (*Otx2*) and gastrulation brain homeobox 2 (*Gbx2*), expressed in the presumptive midbrain and hindbrain, respectively, act co-ordinately with fibroblast growth factor 8 (*Fgf8*) to prevent mixing of cells across the mid-hindbrain boundary. Expressed immediately anterior to *Fgf8*, wingless-type MMTV integration site family, member 1 (*Wnt1*) is essential for midbrain and cerebellum development through its activation of *Fgf8*. Notwithstanding the role of the isthmus as the most well-known organiser of the mid/hindbrain region, the roof plate of rhombomere 1 largely gives rise to the choroid plexus and produces bone morphogenetic protein (BMP) and WNT signals that pattern the dorsal neural tube, including the rhombic lip in mouse.

Normal cerebellar growth and morphogenesis depends on the integrity of the primary cilium that functions as a cellular ‘antenna’. Although most cells possess primary cilia, other cell types possess specialised motile, or nonmotile, cilia. The primary cilium acts as a signalling hub, best known for its role in transducing signalling by the diffusible morphogen sonic hedgehog (SHH).

In the mouse, cells at the midline of the cerebellar anlage release signals that are required for the fusion of the cerebellar hemispheres and for the growth of the vermis that occupies the midline of the mature cerebellum.

In the mouse, a specialised group of roof plate cells induced by the isthmic organiser termed the isthmic node come to occupy the cerebellar midline, from which they have been proposed to control the growth and patterning of the developing vermis scRNA-seq revealed that these cells have the genetic signature of an organising centre; they are enriched for *Wnt* pathway genes, coexpress *Fgf17*, and signal to surrounding cells of the prospective vermis to induce their proliferation. These findings are consistent with earlier mouse genetic knockout studies, which demonstrated a requirement for *Fgf17* and *Fgf8* for the growth of the vermis, distinct from midbrain–hindbrain boundary specification. Furthermore, a broader network additionally involving *Gbx2*, *Otx2*, and the chromatin modifier chromodomain helicase DNA binding protein 7 (CHD7) has been found to link midbrain–hindbrain boundary specification with downstream FGF signalling by cerebellar midline cells in mouse.

In keeping with the aforementioned findings, in humans, a 2.3-Mb deletion of chromosome 8p21.2–21.3 proximal to *FGF17* leads to a marked reduction in *FGF17* expression and is associated with vermis hypoplasia (Dandy–Walker malformation). In the X-linked Opitz syndrome, characterised by cerebellar midline defects, including vermis hypoplasia, the mutated gene, midline 1 (*MID1*), which encodes a ubiquitin ligase, lies genetically upstream of *FGF17*. Therefore, distinct genetic programmes confined to specific cell types and locations regulate cerebellar vermis and hemisphere development. Although mouse models of vermis hypoplasia are informative, human vermis development has additional unique features that are not adequately reflected by these models. In contrast to the mouse, the rhombic lip in humans persists throughout gestation, eventually contributing granule progenitors to the posterior vermis. Sporadic vermis hypoplasia in humans is associated with intellectual and motor deficits and is now known to be strongly linked to a failure of late expansion of the rhombic lip.

The GABAergic neurons are derived from progenitors in the ventricular zone, which express the proneural gene *Ptf1a*.

The mossy and climbing fiber neurons originate from progenitors in the hindbrain rhombic lip that express *Atoh1* or *Ptf1a*

**GENETIC BASES OF KNOWN CEREBELLAR DISORDERS**

1. Cerebellar Vermis Hypoplasia (CVH): is characterized by a small hypoplastic cerebellum with the vermis more affected than the hemispheres.
2. Dandy-Walker malformation (DWM): the most common cerebellar malformation with an estimated incidence of approximately 1 to 5,000. It includes CVH; however, there is also an upward rotation of the cerebellar vermis that results in an enlarged fourth ventricle and an increased size of the posterior fossa.
3. Joubert syndrome and related disorders:are the autosomal recessive disorders and are rare with incidence estimated to be 1/100,000. Characterized by CVH plus the presence of elongated cerebellar peduncles and a deepened interpeduncular fissure that appear as a “molar tooth” on axial brain scans.
4. Cerebellar Hypoplasia: Cerebellar hypoplasia is characterised by a reduced cerebellar volume due to the maldevelopment of one or both hemispheres and a small but normally shaped vermis. This heterogeneous condition is associated with trisomies 9, 13 and 18, congenital disorders of glycosylation, anticonvulsant drugs (valproic acid) or cocaine.

**Causative Genes in Human Cerebellar Malformations**

1. Pancreas specific transcription factor 1a (Ptf1a): the loss of Ptf1a causes a failure to generate GABAergic cerebellar anlage in both human and mouse. Since Purkinje cells, which are GABAergic are also required for the proliferations of cerebellar granule neurons, human and mice lacking Ptf1a exhibit profound cerebellar agenesis.
2. Heterozygous loss of the ZIC1 and ZIC4 genes encoding zinc finger transcription factors can cause DWM.
3. Loss of Foxc1, a signaling molecule causes adjacent cerebellar rhombic lip to lose Atoh1 (Math1) expression, a gene critical for normal granule cell differentiation.

**CONCLUSION**

The current understanding of the molecular and genetic basis of cerebellar development is derived primarily from the study of spontaneous and targeted mouse mutants. Only recently have human patients with cerebellar malformations begun to contribute to the discovery of genes that regulate the development of the cerebellum.

**REFRENCES**

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