DEVELOPMENTAL GENETICS OF THE CEREBELLUM AND GENETIC BASIS OF CEREBELLAR DISORDERS

EKELE PRAISE ENECHOJO

AFEBABALOLA UNIVERSITY

ABSTRACT

The cerebellum represents 10% of the brain's total volume, but contains more than half of our neurons. It acts as a coordination centre, using sensory inputs from the periphery to fine-tune our movement and balance. It is one of the first structures in the brain to begin to differentiate, but one of the last to mature, and its cellular organization continues to change for many months after birth. The study of mouse homologues of Drosophila genes has provided valuable insights into the molecular basis of cerebellar development.

In humans, 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 IO 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 (PCs), Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium. PCs are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, PCs develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including Wnt3. Various growth factors are required for PC 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 PCs. PCs 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.

The cerebellum is one of the first brain structures to begin to differentiate, yet it is one of the last to achieve maturity — the cellular organization of the cerebellum continues to change for many months after birth. This protracted developmental process creates a special susceptibility to disruptions during embryogenesis and makes the cerebellum highly amenable to study. Over the past few years, genetic research has provided a great deal of information about the molecular events directing the formation of the cerebellum. Knowledge of these mechanisms should enable us to address the nature of human diseases that have their root in developmental processes.
Over three decades have passed since Marie Joubert described the original proband for Joubert syndrome, a rare neurological disorder featuring absence of the cerebellar vermis (i.e. midline). Efforts at deciphering the molecular basis for this disease have been complicated by the clinical and genetic heterogeneity as well as extensive phenotypic overlap with other syndromes. However, progress has been made in recent years with the mapping of three genetic loci and the identification of mutations in two genes, AHI1 and NPHP1. These genes encode proteins with some shared functional domains, but their role in brain development is unclear. Clues may come from studies of related syndromes, including Bardet-Biedl syndrome and nephronophthisis, for which all of the

encoded proteins localize to primary cilia. The data suggest a tantalizing connection between intraflagellar transport in cilia and brain development.

References

- Cited by 35 articles

- Deconstructing cerebellar development cell by cell.
- van Essen MJ, et al. PLoS Genet. 2020. PMID: 32298260 Free PMC article. Review.
- Zebrafish dscaml1 Deficiency Impairs Retinal Patterning and Oculomotor Function.
- Ma M, et al. J Neurosci. 2020. PMID: 31685652 Free PMC article.
- Mutant Ahi1 Affects Retinal Axon Projection in Zebrafish via Toxic Gain of Function.
- Zhu L, et al. Front Cell Neurosci. 2019. PMID: 30949029 Free PMC article.
- Mice with a conditional deletion of Talpid3 (KIAA0586) - a model for Joubert syndrome.
- Bashford AL, et al. J Pathol. 2019. PMID: 30924151 Free PMC article.
- Ciliary and cytoskeletal functions of an ancient monooxygenase essential for bioactive amidated peptide synthesis.
- Kumar D, et al. Cell Mol Life Sci. 2019.

PMID: 30879092