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ASSIGNMENT

Write a concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorders.

ANSWER

DEVELOPMENTAL GENETICS OF THE CEREBELLUM AND GENETIC BASES OF KNOWN CEREBELLAR DISORDERS

The cerebellum ('little brain') resides at the anterior end of the hindbrain and is classically defined by its role in sensory-motor processing (Buckner, 2013). In humans it contains over half of the mature neurons in the adult brain (Butts et al., 2012). This morphological complexity belies histological simplicity: the cerebellar cortex is composed of a very basic structure comprising a monolayer of inhibitory Purkinje cells sandwiched between a dense layer of excitatory granule cells and a sub-pial molecular layer of granule cell axons and Purkinje cell dendritic trees. Granule cells receive inputs from outside the cerebellum and project to the Purkinje cells, the majority of which then project to a variety of cerebellar nuclei in the white matter. A less well-defined complement of locally interacting inhibitory interneuron cell types and glutamatergic unipolar brush cells complete the circuit, which famously promised to be the first of any vertebrate neural network to be fully comprehended (Eccles et al., 1967).

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 arbores 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 ephrin's 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 various cerebellar disorders and their genetic bases are given in the table below.

Cerebellar malformations	**Implicated human genes**	**Likely disrupted process**
1) Cerebellar vermis hypoplasia (CVH)	OPHN1: Oligophrenin 1 (OPHN1) gene mutation causes syndromic X-linked mental retardation with epilepsy, rostral ventricular enlargement and cerebellar hypoplasia.	Spine morphogenesis
2) Dandy–Walker malformation (DWM)	ZIC1, ZIC4: Heterozygous deletion of the linked genes ZIC1 and ZIC4 is involved in Dandy–Walker malformation., FOXC1: FOXC1 is required for	Granule cell differentiation

	normal cerebellar development and is a major contributor to chromosome 6p25.3 Dandy-Walker malformation.	
3) Joubert syndrome and related disorders (JSRD)	AHI1: Mutations in the AHI1 gene, encoding jouberin, cause Joubert syndrome with cortical polymicrogyria, ARL13B: Mutations in the cilia gene ARL13B lead to the classical form of Joubert syndrome , CCD2A: CC2D2A is mutated in Joubert syndrome and interacts with the ciliopathy-associated basal body protein, CEP290: Mutations in CEP290, which encodes a centrosomal protein, cause pleiotropic forms of Joubert syndrome,INPP5E: INPP5E mutations cause primary cilium signalling defects, ciliary instability and ciliopathies in human and mouse , NPHP1: NPHP1 gene deletion is a rare cause of Joubert syndrome related disorders,RPGRIP1L, and TMEM67.	Granule cell proliferation
4) Pontocerebellar hypoplasia (PCH)	CASK: Mutations of CASK cause an X-linked brain malformation phenotype with microcephaly and hypoplasia of the brainstem and cerebellum , RARS2: Deleterious mutation in the mitochondrial arginyl-transfer RNA synthetase gene is associated with pontocerebellar hypoplasia , TSEN54, TSEN34, and TSEN2: tRNA splicing endonuclease mutations cause pontocerebellar hypoplasia.	Spine development, cell proliferation, tRNA splicing, cellular maintenance.

REFERENCES:

- Wang, V., Zoghbi, H. Genetic regulation of cerebellar development. Nat Rev Neurosci 2, 484–491 (2001). https://doi.org/10.1038/35081558
- Novel Approaches to Studying the Genetic Basis of Cerebellar Development by Samin A. Sajan, Kathryn E. Waimey, and Kathleen J. Millen
- Development of the cerebellum: simple steps to make a ‘little brain’ by Thomas Butts, Mary J. Green, Richard J. T. Wingate