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

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 organisation continues to change for many months after birth.

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. Otx_2 and Gbx_2 are critical to isthmus organizer development. Otx_2 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 repressive interactions at this 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 fibers into the cerebellar anlage. During final maturation process, 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 cells survival, including nerve growth factor, acetylcholine, 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/Zipol, Zic1 and Zic3. RU49/zipol and Zic1 are thought to be involved in cell poliferation, which requires interaction with the purkinje cells. Purkinje cells might release a diffusible factor such as sonic hedgehog (Shh), and Zic1 could control cell proliferation by indirectly regulating 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, Wnt 7b, 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.

=Source: Nature Reviews neuroscience

Writers: Vincent Y. Wang & Huda Y. Zoghbi

Highlighted the genetic causes of known cerebellar disorders

Cerebellar ataxias are progressive neurodegenerative disorders characterised by atrophy of the cerebellum leading to motor dysfunction, balance problems, and limb and gait ataxia. These include among others, the dominantly inherited spinocerebellar ataxias, recessive cerebellar ataxias such as Friedreich's ataxia, and X-linked cerebellar ataxias.

= Source: sciencedirect.com

More than one dozen hereditary ataxias are caused by repeat expansions. A newly discovered expansion may be the first known common genetic cause of late-onset ataxia says (nature.com)

= Source: Nature Genetics (nature.com)

Writers: Vikram Shakkottai & Henry Paulson