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MEDICINE AND SURGERY

300 LEVEL

NEUROANATOMY

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

ANSWER

The cerebellum, which stands for “little brain”, is a structure of the central nervous system and is a major feature of the hindbrain of all vertebrates. It has an important role in motor control, with cerebellar dysfunction often presenting with motor signs. In particular, it is active in the coordination, precision and timing of movements, as well as in motor learning.

The cerebellum develops from the rhombencephalon (which is the most caudal segment of the embryonic brain). The specific rhombomeres from which the cerebellum forms are rhombomere 1 (Rh.1) caudally and the "isthmus" rostrally.

Two primary regions are thought to give rise to the neurons that make up the cerebellum. The first region is the ventricular zone in the roof of the fourth ventricle (this area produces Purkinje cells and deep cerebellar nuclear neurons). These cells are the primary output neurons of the cerebellar cortex and cerebellum. The second germinal zone (cellular birthplace) is known as the Rhombic lip, neurons then move by human embryonic week 27 to the external granular layer. This layer of cells found on the exterior of the cerebellum produces the granule neurons. The granule neurons migrate from this exterior layer to form an inner layer known as the internal granule layer. The external granular layer ceases to exist in the mature cerebellum, leaving only granule cells in the internal granule layer.

The Engrailed-2 gene is a major actor of the specification of cerebellar cell types and late embryogenic morphogenesis. Math1, expressed by the rhombic lip, is required for the genesis of glutamatergic neurons. Mutants deficient for the

transcription factor Ptf1a display a lack of Purkinje cells and gabaergic interneurons. Rora (Retinoic-Acid-Related Orphan Receptor Alpha) gene contributes to the developmental signalling between granule cells and Purkinje neurons.

The Engrailed-2 Gene: The engrailed (En) homeobox transcription factor family is critical for the patterning of cerebellar lobules and for Purkinje cells protein stripes. The En1/2 regulates the targeting of mossy fiber systems to subsets of cerebellar lobules, showing a main role for the afferent topography in the cerebellar circuitry (Sillitoe et al., 2010). Initially, the En1/2 mRNA/protein are expressed in the ventricular zone. During early post-natal cerebellogenesis, En1/2 are expressed in spatially restricted patterns in most cell types

Math1: The specification and differentiation of glutamatergic lineages is dependent upon Math1, a transcription factor of the bHLH class. Math1 is critical for the proper development of the granular layer of the cerebellum. Mice deficient in Math1 show a loss of glutamatergic neurons in cerebellar nuclei, a loss of external granular layer and unipolar brush cells. In addition, Math1 null embryos lack interneurons giving rise to the spinocerebellar and cuneocerebellar tracts (Bermingham et al., 2001).

Ptf1a and Ascl1: Cerebelless mutants have a deficit in the transcription factor Ptf1a (pancreatic transcription factor 1a). They show a lack of Purkinje cells and gabaergic interneurons. It has been demonstrated that climbing fiber neurons are derived from the Ptf1a domain (Yamada et al., 2007). In Ptf1a null mutants, immature climbing fiber neurons cannot migrate or differentiate, causing a failure in the formation of the inferior olivary nucleus. Ptf1a is also involved in the control of fate and survival of neurons during development. In human, mutations of Ptf1a are associated with cerebellar agenesis.

Ascl1 directs ventricular neuroepithelium progenitors toward inhibitory interneuron fate and suppresses the astrocytic differentiation. Mice lacking Ascl1 in the cerebellum exhibit a major decrease of cerebellar interneurons and an imbalance between oligodendrocytes and astrocytes.

Rora (Retinoic-Acid-Related Orphan Receptor Alpha) Gene: Rora is a transcription factor encoding a retinoid-like nuclear receptor which is highly

expressed in the cerebellum. Rora belongs to the steroid-thyroid hormone receptor superfamily. Its endogenous ligand is cholesterol which is abundantly present in each cell. Therefore, Rora acts as if it is a constitutively active nuclear receptor. It was initially thought that Rora was exclusively expressed in neurons, but recent data show that it is also expressed in glial cells especially in astrocytes. Rora plays a pivotal role in the development of the cerebellum, olfactory bulb, and retina. However, its functions extend beyond development. For instance, Rora also protects neurons against oxidative stress and shows an anti-inflammatory action by inhibiting the NF-Kappa-B pathway.

The autosomal recessive staggerer mutation is associated with a severe degeneration of Purkinje neurons with a nearly total absence of granule cells at the end of the first postnatal month. The homozygous mouse Rorasg/Rarasg is highly ataxic, whereas the heterozygous mouse Rora+/Rarasg appears phenotypically normal, showing disabilities during challenging tasks.

Cerebellar disorder and genetic bases:

ATAXIA: Ataxia is a neurological sign consisting of lack of voluntary coordination of muscle movements that can include gait abnormality, speech changes, and abnormalities in eye movements.

Mutations in the APTX, SETX, or PNKP gene cause ataxia with oculomotor apraxia types 1, 2, or 4, respectively. The APTX, SETX, and PNKP genes provide instructions for making proteins that are involved in repairing damaged DNA. Mutations in any of these genes reduce the amount of functional protein produced from that gene. This shortage prevents the efficient repair of DNA damage, which leads to the accumulation of broken DNA strands. DNA breaks may be caused by potentially harmful molecules (called reactive oxygen species) produced during normal cellular functions, natural and medical radiation, or other environmental exposures. They may also occur when chromosomes exchange genetic material in preparation for cell division. DNA damage that is not repaired makes the cell unstable and can lead to cell death. It is thought that cell death has a particularly severe effect in the brain because the nervous system does not replace nerve cells that have been lost. The part of the brain involved in coordinating movements (the cerebellum) is especially at risk. It is thought that the loss of brain cells in the

cerebellum causes the movement problems characteristic of ataxia with oculomotor apraxia.

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