MATRIC NUMBER: 17/MHS01/033

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LEVEL: 300LEVEL

DEPARTMENT: MEDICINE AND SURGERY

COURSE TITLE: NEUROANATOMY

COURSE CODE: ANA303

ASSIGNMENT TITLE: CEREBELLUM AND ITS CONNECTIONS

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QUESTION:

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

ANSWER:

The cerebellum represents about 10% of the brain's total volume, but contains more than half of total neurons. It acts as a coordination center, using sensory inputs from the periphery to fine-tune 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 internal structure of the cerebellum itself, displays a conflicting design. It is relatively simple and repeated throughout externally, yet the connections between its neurons is desirably complex, displaying a bevy of gene expression domains and functional circuits. The developmental mechanisms that coordinate the establishment of cerebellar structure and circuitry provide a powerful model for understanding how functional brain networks are formed.

Two primary germinal zones, the germinal matrices, generate the cells that make up the cerebellum. Each zone expresses a specific set of genes that establish the cell lineages within the cerebellar anlage. Then, cohorts of differentiated projection neurons and interneuron progenitors migrate into the developing cerebellum.

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.

In mice however, the cerebellum is developed from the mesencephalon and metencephalon. 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. Purkinje cells are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, 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 cell 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 Purkinje cells. Purkinje cells 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.

After this, a number of remarkable patterning events occur including:

i. Transformation of the smooth cerebellar surface into an intricately patterned series of folds

ii. Formation of three distinct cellular layers

iii. Demarcation of parasagittal gene expression domains.

Together, these structural and molecular organizations are thought to support the proper connectivity between incoming afferent projections and their target cells.

After birth, genetic programs and neural activity repattern synaptic connections into topographic neural networks called modules, which are organized around a longitudinal zone plan and are defined by their molecular, anatomic, and functional properties.

GENETIC BASES OF KNOWN CEREBELLAR DISORDERS.

1. Joubert syndrome and related disorders (JSRD): It is a rare neurological disorder featuring absence of the cerebellar vermis (i.e. midline). It shares phenotypic symptoms with other syndromes.

It is caused by mutations in AHI1, NPHP1, ARL13B, CCD2A, CEP290, INPP5E, RPGRIP1L or TMEM67. Mutation in any one or more of these genes causes a disruption in granule cell proliferation.

2. Cerebellar Vermis Hypoplasia (CVH): caused by an implication of OPHN1 gene. Causes a disruption in spine morphogenesis.

3. Pontocerebellar hypoplasia (PCH): implication in CASK, RARS2, TSEN54, TSEN34, and TSEN2 genes, leading to a disruption in spine development, cell proliferation, tRNA splicing and/or cellular maintenance.

4. Dandy-Walker Malformation (DWM): implication of ZIC1, ZIC4 or FOXC1 genes, leading to a disruption in granule cell proliferation.

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