Neuroanatomy

Name: Okafor Vanessa
Matric number: 17/mhs01/242
Department: Medicine and surgery
Course: Neuroanatomy

Question : Write a concise review on the developmental genetics of the cerebellum and highlight the genetic basis of known cerebellar disorders

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 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. Thereafter, a number of remarkable patterning events occur including transformation of the smooth cerebellar surface into an intricately patterned series of folds, formation of three distinct cellular layers, and the 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.

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.

GENETIC BASES OF KNOWN CEREBELLAR DISORDERS

DANDY-WALKER MALFORMATION (DWM)

It is a rare congenital brain malformation in which the part joining the two hemispheres of the cerebellum (the cerebellar vermis) does not fully form, and the fourth ventricle and space behind the cerebellum (the posterior fossa) are enlarged with cerebrospinal fluid.

Dandy-Walker malformation has also been associated with many chromosomal abnormalities. This condition can be a feature of some conditions in which there is an extra copy of one chromosome in each cell (trisomy). Dandy-Walker malformation most often occurs in people with trisomy 18.

Dandy-Walker malformation can also be a feature of genetic syndromes that are caused by mutations in specific genes.

CEREBELLAR HYPOPLASIA

Cerebellar hypoplasia is a neurological condition in which the cerebellum is smaller than usual or not completely developed. It is believed that the cerebellar hypoplasia is due to a defect in the neuronal proliferation and neuronal migration during development of the embryonic nervous system. It may result after an atrophy (destruction) of the cerebral cortex on the opposite side.

The oligophrenin 1 gene (OPHN1) is a protein with a Rho-GTPase-activating domain required in the regulation of the G-protein cycle. Mutations in the OPHN1 cause X-linked mental retardation (XLMR) with cerebellar hypoplasia and distinctive facial appearance.

JOUBERT SYNDROME

Joubert syndrome (JS) is an autosomal recessive neurodevelopmental disorder, which is characterized by the molar tooth malformation (MTM), a complex brainstem malformation that reflects aplasia or marked hypoplasia of the cerebellar vermis, thickened and elongated superior cerebellar peduncles and a deepened interpeduncular fossa at the midbrain–hindbrain junction.

Ten genes have been identified that cause Joubert syndrome. A mutation in the AHI1 (JBTS3) gene is responsible for this condition in approximately 11% of families. Affected individuals with this gene mutation often have impaired vision due to retinal dystrophy. A mutation in the NPHP1 (JBTS4) gene causes approximately 1-2% of Joubert syndrome. Affected individuals

with this gene mutation often develop a progressive kidney disease called nephronophthisis. A mutation in the CEP290 (JBTS5) gene causes about 4-10% of Joubert syndrome. Mutations in the TMEM67 (JBTS6), JBTS1, JBTS2, JBTS7, JBTS8 and JBTS9 genes are also associated with Joubert syndrome. Other genes responsible for this condition are currently unknown.