NAME: ERUVWETOPHURE JEMILAND

MATRIC NO: 17/MHS01/121

DEPARTMENT: MBBS

LEVEL: 300l

TITLE: CEREBELLAR CONNECTIONS (NEUROANATOMY)

DEVELOPMENTAL GENETICS OF THE CEREBELLUM

The cerebellum is a member of the rhombencephalon and it is ovoid structure located the posterior cranial fossa inferior to the tentorium cerebelli. The internal structure of the cerebellum reflects an intriguing paradox; its cytoarchitecture is relatively simple and repeated throughout, yet the connections between its neurons are wired into a complex array 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 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 different genes that contribute to the development of the cerebellum include;

* **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.

* **Math1**

Math1 is critical for the proper development of the granular layer of the cerebellum. In addition, Math1 null embryos lack interneurons giving rise to the spinocerebellar and cuneocerebellar tracts.

* **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. 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.

* **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.

GENETIC BASIS OF KNOWN CEREBELLAR DISORDERS

* Joubert syndrome is a disorder that present with developmental delay, hypotonia, impaired respiration, abnormal eye movements, and ataxia. Motor learning is strongly impaired. Joubert syndrome is associated with mutations of genes encoding components of the primary cilia.
* Another disorder clearly associated with learning disabilities is rhombencephalosynapsis, a malformation of the hindbrain characterized by fusion of the cerebellar hemispheres and dentate nuclei. It is assumed that the disorder is due to a failure of dorsal patterning at the midbrain-hindbrain boundary.
* Autism spectrum disorders are characterized by difficulties in communication, social skills, and repetitive behavior. Cerebellar networks might be critically involved in the pathogenesis of autism. An immune dysfunction with local inflammation contributes to the pathogenesis of autism. The expression of IL-6 is increased in the cerebellum of autistic patients. IL-6 impacts upon the development of the cerebellum, impairing neural cell adhesion, migration, and causing an excessive formation of excitatory synapse.

References;

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