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**Course; Neuroanatomy**

**Cerebellum and Its Connections.**

**QUESTION**

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

**ANSWER**

**ABSTRACT**

The study of both spontaneous and engineered mutant mouse have made easy the study of cerebellar developments. Improvements in brain imaging such as magnetic resonance imaging (MRI) and the emergence of better classification schemes for human cerebellar malformations have recently led to the identification of a number of genes which cause human cerebellar disorders.

**INTRODUCTION**

The study of spontaneous neurological mouse mutants aided many initial discoveries concerning cerebellar developments. Significant advances in mouse genetics have allowed for more targeted studies using engineered gene knockouts and transgenic mice. These mice have facilitated the examination of more subtle phenotypes such as mild behavioral abnormalities and small disruptions in cerebellar circuitry. Genetics has recently enabled the identification of genes **causing human pontocerebellar hypoplasia, Joubert syndrome and Dandy-Walker malformation (DWM).** When combined with studies in mouse, a variety of molecular mechanisms, including transcriptional regulation, mitochondrial function and ciliary signaling have been implicated in homeostasis, pattering and cell proliferation during cerebellar development. Here we discuss these issues and advocate the integrated use of human and mouse systems to further explain the basis of cerebellar development.

**DISCUSSION**

The cerebellum has essential roles in motor coordination, but is not essential for viability. It is one of the first brain structures to differentiate, yet it is one of the last to receive maturity and its cellular organization continues to change for many months after birth The cerebellum arises from both the mesencephalic and rhombencephalic vesicles of the neural tube and develops over a relatively long period of time between early embryogenesis and late childhood. Development of the cerebellum can be described in four basic stages. In the first stage, characterization of cerebellar territory occurs at the midbrain–hindbrain boundary. Transplantation studies in chicken and mouse have found that the isthmus organizer (IsO), a region corresponding to the midbrain–hindbrain boundary expression, is crucial for specifying midbrain and cerebellar structures. At the isthmus, restricted expression of secreted factors, such as fibroblast growth factor 8, FGF8 and Wnt1, the mammalian homolog of Drosophila wingless gene, as well as homeobox proteins En1 and En2 and paired box genes Pax2 and Pax5 are required for early specification of midbrain and hindbrain structures. In the second stage, two compartments for cell proliferation are formed. Purkinje cells and cells of the deep cerebellar nuclei are generated in the roof of the fourth ventricle, and granule cell precursors, as well as cells of the precerebellar nuclei are formed in the rhombic lip. Development of Purkinje cells is not well understood, but they are known to secrete Sonic hedgehog which regulates proliferation of granule cells. By this time point, granule neuron precursors express a number of markers, Math1, nestin, zipro1/RU49 and Zic genes 1, 2. Purkinje cells migrate radially to their final positions, whereas granule neurons migrate over the surface of the developing cerebellum, forming the external granule layer (EGL). In the third stage, cells of the EGL migrate inward along the processes of Bergman glia to their final position in the internal granular layer (IGL). Finally, cerebellar circuitry is established and further differentiation occurs. The lower portion of the rhombic lip also gives rise to cells of the precerebellar nuclei such as the inferior olivary nuclei, which migrate to positions in the brainstem.

**Types of Human Cerebellar Malformations**

1. Cerebellar Vermis Hypoplasia (CVH): is characterized by a small hypoplastic cerebellum with the vermis more affected than the hemispheres.
2. Dandy-Walker malformation (DWM): the most common cerebellar malformation with an estimated incidence of approximately 1 to 5,000. It includes CVH; however, there is also an upward rotation of the cerebellar vermis that results in an enlarged fourth ventricle and an increased size of the posterior fossa.
3. Joubert syndrome and related disorders:are the autosomal recessive disorders and are rare with incidence estimated to be 1/100,000. Characterized by CVH plus the presence of elongated cerebellar peduncles and a deepened interpeduncular fissure that appear as a “molar tooth” on axial brain scans.
4. Cerebellar Hypoplasia: Cerebellar hypoplasia is characterised by a reduced cerebellar volume due to the maldevelopment of one or both hemispheres and a small but normally shaped vermis. This heterogeneous condition is associated with trisomies 9, 13 and 18, congenital disorders of glycosylation, anticonvulsant drugs (valproic acid) or cocaine.

**Causative Genes in Human Cerebellar Malformations**

1. Pancreas specific transcription factor 1a (Ptf1a): the loss of Ptf1a causes a failure to generate GABAergic cerebellar anlage in both human and mouse. Since Purkinje cells, which are GABAergic are also required for the proliferations of cerebellar granule neurons, human and mice lacking Ptf1a exhibit profound cerebellar agenesis.
2. Heterozygous loss of the ZIC1 and ZIC4 genes encoding zinc finger transcription factors can cause DWM.
3. Loss of Foxc1, a signaling molecule causes adjacent cerebellar rhombic lip to lose Atoh1 (Math1) expression, a gene critical for normal granule cell differentiation.

**CONCLUSION**

The current understanding of the molecular and genetic basis of cerebellar development is derived primarily from the study of spontaneous and targeted mouse mutants. Only recently have human patients with cerebellar malformations begun to contribute to the discovery of genes that regulate the development of the cerebellum.

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