THE CEREBELLUM:

ITS DEVELOPMENTAL GENETICS AND THE GENETIC BASES OF SOME CEREBELLAR DISORDERS

BY

OKOLO AWELE CHRISTABEL

17/MHS01/244

COURSE CODE: ANA 303(NEUROANATOMY)

LECTURER: MR EDEM

DATE: 10TH JULY, 2020

Abstract

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.

Introduction

OVERWIEW OF CEREBELLER DEVELOPMENT AND JOUBERT SYNDROME

Understanding of cerebellar development provides some insights into the pathogenesis of ***Joubert syndrome(JS).*** 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.

Bardet–Biedl syndrome and IFT

Bardet–Biedl syndrome (BBS) is characterized by obesity, mental retardation, polydactyly, gonadal malformation, retinal dystrophy and renal dysfunction. Neurological malformations are unusual, but cerebellar abnormalities have been reported in the literature and, in particular, a case of CVH has been documented in a patient with BBS. Although not reported to be present, we found clear evidence of the MTM in the MRI data for this patient, suggesting a link between BBS and JS. Eight genes, BBS1–BBS8, have been identified to date and all of the encoded proteins have been localized to cilia and/or implicated in ciliary function and assembly,

including cytoskeletal reorganization and cytokinesis. In particular, BBS4 has been associated with components of IFT, a microtubule-dependent mechanism by which components are trafficked during assembly and maintenance of cilia and flagella. IFT was discovered first in Chlamydomonas, but has subsequently been shown to be conserved in other species. Loss-of-function studies in C. elegans have also shown the requirement of BBS genes in this process. Mutations in bbs-7 and bbs-8 orthologs result in shortened cilia with impaired chemosensory ability and almost complete loss of movement of some known IFT molecules.

CONCLUSION

Joubert syndrome (JS) is a part of a spectrum of developmental disorders with a complex midbrain–hindbrain malformation as well as involvement of other systems—renal, retinal and/or hepatic. Mutations of AHI1 have recently been shown to cause a form of JS, but the function of this gene is currently unknown. However, it is interesting to find that genes associated with related disorders all seem to encode proteins involved in cilia function or assembly, suggesting an interesting link between cilia and cerebellar development. It is tempting to speculate that genes involved in JS may also be involved in cilia or in mediating cilia-dependent signals

References

1. Wiley Interdiscip Rev Dev Biol . Jan-Feb 2013;2(1):149-64. doi: 10.1002/wdev.65.
2. Maria, B.L., Hoang, K.B., Tusa, R.J., Mancuso, A.A., Hamed, L.M., Quisling, R.G., Hove, M.T., Fennell, E.B., Booth-Jones, M., Ringdahl, D.M. et al. (1997) 'Joubert syndrome' revisited: key ocular motor signs with magnetic resonance imaging correlation. J. Child Neurol., 12, 423–430.
3. Maria, B.L., Boltshauser, E., Palmer, S.C. and Tran, T.X. (1999) Clinical features and revised diagnostic criteria in Joubert syndrome. J. Child Neurol., 14, 583–590; discussion 590–591.