ASSIGNMENT ON NEUROANATOMY

CEREBELLUM AND ITS CONNECTIONS

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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

The cerebellum (‘little brain’) resides at the anterior end of the hindbrain and is classically defined by its role in sensory-motor processing (Buckner, 2013). In amniotes, it represents one of the most architecturally elaborate regions of the central nervous system (CNS), and in humans it contains over half of the mature neurons in the adult brain (Butts et al., 2012). This morphological complexity belies histological simplicity: the cerebellar cortex is composed of a very basic structure comprising a monolayer of inhibitory Purkinje cells sandwiched between a dense layer of excitatory granule cells and a sub-pial molecular layer of granule cell axons and Purkinje cell dendritic trees. Granule cells receive inputs from outside the cerebellum and project to the Purkinje cells, the majority of which then project to a variety of cerebellar nuclei in the white matter. A less well-defined complement of locally interacting inhibitory interneuron cell types and glutamatergic unipolar brush cells complete the circuit, which famously promised to be the first of any vertebrate neural network to be fully comprehended (Eccles et al., 1967).

DISCUSSION

The cerebellum is one of the first brain structures to begin to differentiate, yet it is one of the last to achieve maturity and its cellular organisation continues to change for many months after birth. Over the past few years, genetic research has provided a great deal of information about the molecular events directing the formation of the cerebellum. The cerebellum represents 10% of the brains 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.

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 specialised germinal matrix called the RHOMBIC LIP.

Cerebellar neurogenesis is compartmentalised in relationship with neurotransmitter fate.

The Engrailed-2-gene is a major actor of the specialisation of cerebellar cell types and late embryonic morphogenesis. The engrailed (En) homebox 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 fibre systems to subsets of cerebellar lobules, showing a main role for the afferent topography in the cerebellar circuitry.

Math 1, expressed by the rhombic lip, is required for the genesis of glutamatergic neurons. It is critical for the proper development of the granular layer of the cerebellum.

Mutants deficient for the transcription factor Ptf1a (pancreatic transcription factor 1a) display a lack of purkinje cells and GABAergic interneurons. It is also involved in the control of fate and survival of neurons during development.

Rora gene (Retinoic Acid Related Orphan Receptor Alpha Gene) contributes to the developmental signalling between granule cells and purkinje neurons. Rora is a transcription factor encoding a retinoid-like unclear receptor which is highly expressed in the cerebellum. It also protects neutrons against oxidative stress and shows an anti-inflammatory action by inhibiting the NF-Kappa-B pathway.

The expression profile of sonic hedgehog in postnatal stages determines the final size/shape of the cerebellum. Sonic hedgehog is a morphogenetic factor which is a masterly in a cerebellar patterning and foliation. Genes affecting the development impact upon the physiological properties of the cerebellar circuits. For instance, receptors are developmentally regulated and

their action interferes directly with developmental processes. Another field of research which is expanding relates to very preterm neonates. They are at risk at cerebellar lesions, which may themselves impair the developmental events. Very preterm neonates often show sensory-motor deficits, highlighting another major link between impaired developments and learning deficiencies. Pathways playing a critical in cerebellar development are likely to become therapeutically targets for several neurodevelopment disorders.

SOME GENETIC BASES OF CEREBELLAR DISORDERS

There is currently a growing awareness that neurodevelopment disorders are associated with cerebellar deficits and learning impairments. Still, the molecular mechanisms of the cerebellar defects remain poorly understood in many cases.

A) **Joubert Syndrome**

The disorder presents with developmental delay, hypotonia, impaired respiration, abnormal eye movements and ataxia. Motor learning is strongly impaired. The 'Molar Tooth Sign' (deep interpeduncular fossa, enlarged superior cerebellar pedants which are more horizontally oriented and hypoblastic cerebellar vermis) is very suggestive. It is associated with mutations of genes encoding components of the primary cilia. Interestingly, primary cilia are determined for sonic hedgehog signal transduction.

Disruption of primary cilia formation blocks the proliferation of neural progenitors of granule cells mediated by sonic hedgehog.

B) **Rhombencephalosynapsis**

It is associated with learning disabilities. It is a malformation of the hindering characterised by fusion of the cerebellar hemispheres and dentate nuclei. An association with mutations in the MN1 gene (meningioma (disrupted in balanced translocation)) 1 has been reported in cases of atypical rhomboencephalosynapsis.

C) **Dandy-Walker Malformation**

Sonic hedgehog might also be involved in the pathogenesis of Dandy-Walker malformation through a contribution of Zinc finger transcription factors which modulate the sonic hedgehog pathway

D) **Autism**

They are characterised by difficulties in communication, social skills and repetitive behaviour. Cerebellar networks might be critically involved in 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 synapses.

E) **Smith-Lemli-Opitz Syndrome**

It is an autosomal recessive syndrome with multiple congenital malformations, which is due to defects of cholesterol homeostasis. Hypoplasia is associated with this syndrome. Blocking GLI2 causes a failure in the development of cerebellar granular near oral precursors, ending in cerebellar hypoplasia.

CONCLUSION

In this mini-review, we have summarized recent advances in our understanding of the molecular mechanism governing cerebellar development. We have discussed the complex interactions between cerebellar development and motor learning. The identification of several pathways which are potential targets for novel therapies in the future, such as cerebellar neurosteroidogenesis, En1/2, Math1, Ptf1a, Rora, or sonic hedgehog, is now bringing hope in a field which has often remained neglected because of a lack of understanding of the molecular events leading to the malformations. There is still a growing need to identify new targets, since neurodevelopmental disorders are heterogeneous and will impact upon the whole life of patients in most cases. Protecting the developing cerebellum—a concept which could be called cerebelloprotection—is now attracting the interest of the scientific community, especially with discoveries of the roles of the cerebellum in cognitive skills. Very preterm neonates are an example of a population of patients at risk and which could benefit from neuroprotecting actions.

REFRENCES

- Pudmed Abstract
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