THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM AND THE GENETIC BASES OF KNOWN CEREBELLAR DISORDERS

A Review of Developmental Genetics of the Cerebellum and the Genetic Bases of known Cerebellar Disorders

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The Developmental Genetics of Cerebellum and the Genetic Bases of known Cerebellar Disorders: A Literature Review

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Abstract

The internal structure of the cerebellum is an intriguing paradox; its cytoarchitecture is relatively simple compared to the connections between its neurons, which are wired into a complex array of gene expression domains and functional circuits. The genetic research of cerebellar development has provided a great deal of information about the molecular events directing the formation of the cerebellum. The developmental mechanisms that coordinate the establishment of cerebellar structure and circuitry provide a powerful model for understanding how a functional brain develops and its significance in cerebellar disorders and diseases. The cellular makeup of the cerebellum is derived from two primary germinal matrices (the ventricular zone and a specialized germinal matrix called the rhombic lip). Each matrix/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. Altogether, structural and molecular organisations are thought to support the proper connectivity between incoming afferent projections and their target cells.
Key words: Cerebellum, circuitry, genetic, development, disorders.

I. 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). Mature, the cerebellum contains more than half of our neurons [2]. The 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 cells axons and Purkinje cell dendritic trees [1]. Granule neurons are glutamate-releasing, excitatory neurons, whereas Purkinje cells are inhibitory, using GABA (γ-aminobutyric acid) as their transmitter. There are three additional classes of cerebellar neurons: Golgi cells, which contain GABA and glycine, and provide feedback inhibition to granule neurons, and the GABA-releasing Stellate and Basket cells, which modulate Purkinje cell output (V. Y. Wang, 2001). In addition to coordinating motion, the cerebellum has been implicated in motor learning and higher cognitive functions,

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but the circuitry involved in these activities is not yet understood. The cerebellum is one of the first brain structures to begin development, yet it is one of the last to achieve maturity [2]. Its extended development into the postnatal period makes this structure vulnerable to a variety of pathologies, including neoplasia [5]. These properties have prompted intensive investigations that reveal not only developmental mechanisms in common with other regions of the neuraxis but also unique strategies to generate neuronal diversity[5].

In this review, we will examine the progress made over the years in understanding cerebellum development and discuss their significance for clinical science. Using insights from genetic studies in mice, sharks, paddlefish, zebrafish, frogs and chicks; we concentrate on human cerebellar development.

II. Overview of Human Cerebellar Development

The most anterior portion of the neural tube is undergoing drastic changes during early development generating, by differential proliferation, three primary brain vesicles: the forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon) (Martínez and Puelles, 2000). The cerebellum differentiates from the dorsal region of the posterior neural tube[6];. The development of cerebellum occurs in four basic steps:

1. Characterization of the cerebellar territory at the midbrain-hindbrain boundary.
2. Formation of two compartments for cell proliferation: first, the Purkinje cells and the deep cerebellar nuclei arise from the ventricular zone of the mesencephalic alar plate; second, granule cell precursors are formed from a second compartment of proliferation, i.e. the upper rhombic lip.
3. Inward migration of the granule cells: granule precursor cells form an external granular layer, from which (and continuing into the first postnatal year), granule cells migrate inwards to their definite position in the internal granular layer.

Formation of cerebellar circuitry and further differentiation [7].

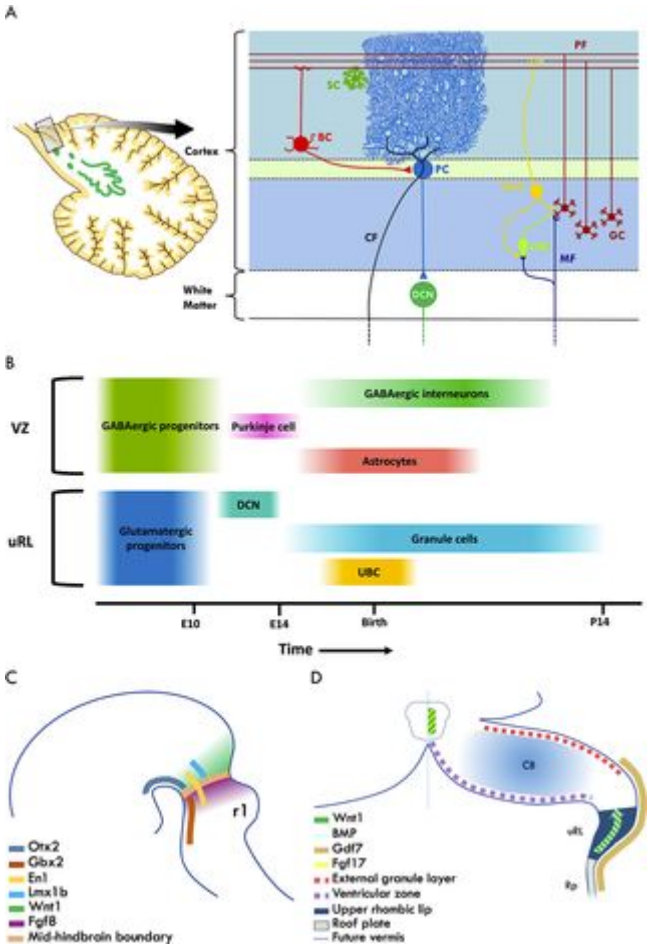

Fig 1. Specification of the CB and the major constituent cell types in mice.
(A) Organisation of cell types in the mature CB. Afferent input is transmitted via MFs and CFs. BC, GoC, SC, and UBC are interneuron subtypes. (B) Progenitors in two germinal zones, the VZ and uRL, produce distinct neuronal and glial cellular subtypes sequentially. (C) The future CB develops immediately posterior to the mid-hindbrain boundary. Patterning genes and secreted molecules involved in specifying this territory are indicated. (D) The Rp and cerebellar midline have important signalling functions that establish distinct regions of the CB, including the uRL and future vermis. BC, basket cell; BMP, bone morphogenetic protein; CB, cerebellum; CF, climbing fibre; DCN, deep cerebellar nuclear neuron; E, embryonic day; En1, engrailed homeobox 1; Fgf8, fibroblast growth factor 8; Fgf17, fibroblast growth factor 17; Gbx2, gastrulation brain homeobox 2; Gdf7, growth differentiation factor 7; GC, granule cell; GoC, Golgi cell; Lmx1b, LIM homeobox transcription factor 1 beta; MF, mossy fibre; Otx2, orthodenticle homeobox 2; P, postnatal day; PC, Purkinje cell; PF, parallel fibre; r1, rhombomere 1; Rp, roof plate; SC, stellate cell; UBC, unipolar brush cell; uRL, upper rhombic lip; VZ, ventricular zone; Wnt1, wingless-type MMTV integration site family, member 1.

4.

Characterization of Cerebellar Territory at the Midbrain-Hindbrain Boundary

The embryonic cerebellum begins as little more than the symmetric bulges into the early fourth ventricle: cerebellar hemispheres arise as mere buds from laminae on either side of the metencephalon produces outgrowths that form the first elements of the cerebellum. These lateral elements develop towards the midline and fuse in a rostral-to-caudal direction. As the primitive hemispheres come into contact with each other, they form first the superior and then the inferior vermis, the lateral elements from the fusion develop into the cerebellar hemispheres. In vertebrates, the common expression border of two homeobox genes, Otx2 and Gbx2,demarcates the prospective midbrain-hindbrain border (MHB) in the neural plate at the end of gastrulation. The presence of a compartment boundary at the MHB has been demonstrated, but the mechanism and timing of its formation remain unclear [8]. Otx2 and Gbx2 act coordinately with fibroblast growth factor 8 (Fgf8) to prevent mixing of cells across the mid-hindbrain boundary. Fgf8 is a diffusible factor that exerts its action partially by inducing the expression of wingless homologue 1 (Wnt 1) through Lim homeobox 1b (Lmx1b) [9,10]. Wnt1, in turn, maintains the expression of Engrailed (En1) [11], which then positively regulates Fgf8 expression, completing the feedback regulatory loop [1]. Wnt1 and Lmx1b probably exert their influence through the action of En1 [10]. En2, a paralogue of En1 might also function in mid-/hindbrain patterning, En2 is expressed shortly after EN1 [2]. The paired box genes Pax2 and Pax5 are expressed in the mid-/hindbrain region [12]

Compartments for Cell Proliferation

Cells in the cerebellum arise from two different germinal matrices. From the ventricular zone (also known as the ventricular germinal matrix), cells radiate laterally and evolve into the deep cerebellar nuclei at about week eight in human embryogenesis. At week nine, the ventricular zone begins to produce cells that will eventually form the Purkinje neurons. By 24 weeks, these proto-purkinje cells send dendrites to the parallel fibres of the granule neurons. The full number of Purkinje cells is present early on , but their mature monolayer forms some time between 16 and 28 weeks postnatally. Purkinje cells continue their maturation after birth, projecting to the deep cerebellar nuclei and refining the input they receive from the climbing fibres of inferior olivary neurons. From the ventricular zone, a third population of neurons is born after the formation of Purkinje cells. These neurons include the stellate, basket and Golgi interneurons that can be found in the molecular layer. These three kinds of neurons have a modulatory action on the Purkinje cells and granule neurons.
Unlike most of the cell types of the cerebellum, which are born at the ventricular zone, cerebellar granule neurons come from a specialized germinal Matrix called the rhombic lip. The rhombic lip (RL) is an embryonic proliferative neuroepithelium that generates several groups of hindbrain neurons. The rhombic lip is located between the fourth ventricle and the metencephalic roof plate. Migration of these primitive cells over the surface of the

cerebellum starts as early as week 11 in humans; neuronal elements are present in the external granular layer by week 27. 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 S*hh* 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.

III. Conclusion

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