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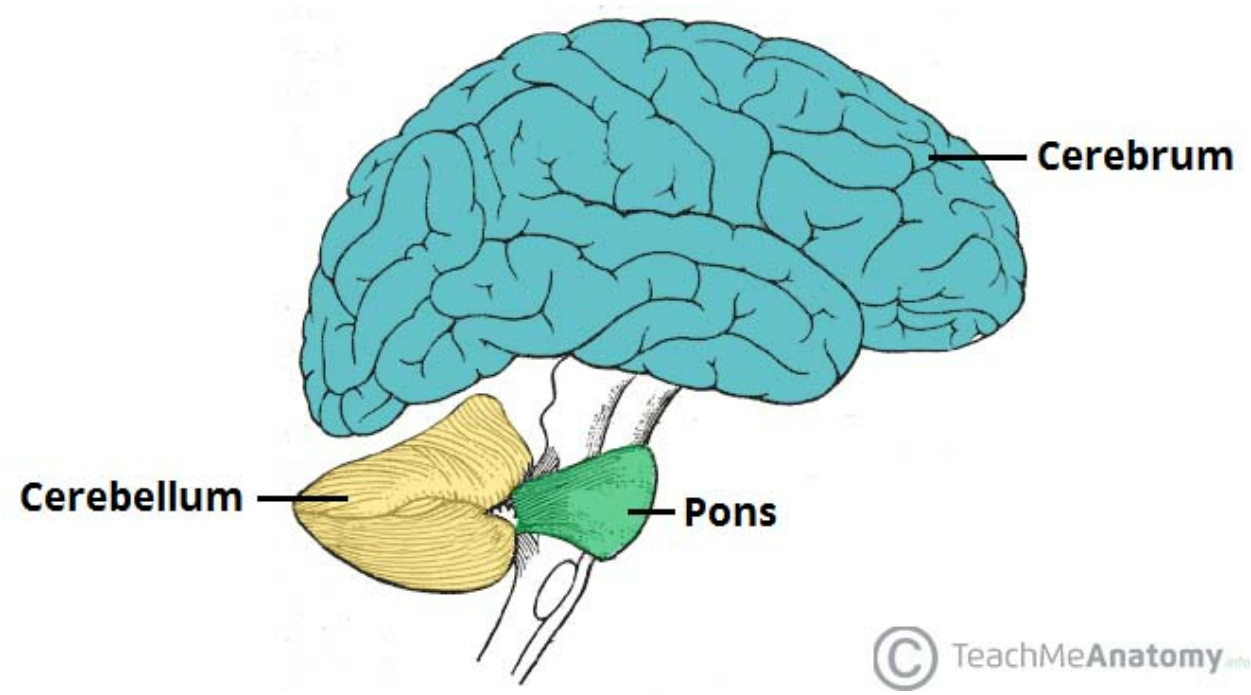
300L MBBS

DEVELOPMENTAL GENETICS OF THE CEREBELLUM



Diagramof the Cerebellum

The cerebellum, which stands for " little brain" , is a structure of the central nervous system It has an important role in motor control, with cerebellar dysfunction often presenting with motor signs. In particular, it is active in the coordination, precision and timing of movements, as well as in motor learning. The cerebellumis located at the back of the brain, immediately inferior to the occipital and temporal lobes, and within the posterior cranial fossa. It is separated fromthese lobes by the tentorium

cerebelli, a tough layer of dura mater

Cerebellumdevelopment

The brain is sometimes divided into the brain stem(mesencephalon, pons from the metencephalon, and myelencephalon) and the higher centres (cerebrum and cerebellum). The brain stemis a direct continuation of the spinal cord thus, distinct basal and alar plates. The cerebellumdevelops fromthe dorsolateral part of the alar lamina of the metencephalon .They are at first two primordia of the cerebellum, right and left. These extend medially in the roof plate of the metencephalon to eventually fuse across the midline. As the cerebellumincreases in size, fissures appear on its surface. The lateral lobes and vermis can soon be distinguished, as a result of differential growth. The developing cerebellumcan be divided into: (a) an intraventricular part that bulges into the cavity of the developing fourth ventricle, and (b) an extraventricular part that is seen as a bulging on the surface. At first the intraventricular part is the larger of the two, but at a later stage, the extraventricular part becomes much larger than the intraventricular part and constitutes almost the whole of the organ. The cerebellum, at first, consists of the usual matrix cell, mantle and marginal layers. Some cells of the mantle layer migrate into the marginal layer to formthe cerebellar cortex. The cells of the mantle layer that do not migrate into the cortex, develop into the dentate, emboliform, globose and fastigal nuclei . The superior cerebellar peduncle is formed chiefly by the axons growing out of the dentate nucleus. The middle cerebellar peduncle is formed by axons growing into the cerebellumfromthe cells of the pontine nuclei, while the inferior cerebellar peduncle is formed by fibres that grow into the cerebellumfrom the spinal cord and medulla

Fromthe ventricular zone, cells radiate laterally and evolve into the deep

cerebellar nuclei and Purkinje cells of the cerebellar cortex. However, the cerebellar granule neurons arise fromthe rhombic lips .Hence, the cerebellar cortex is made up of three layers which are the molecular layer, purkinje cell layer and granular layer. Cells found in these layers are purkinje cells, granule cells, stellate cells, basket cells and golgi cells

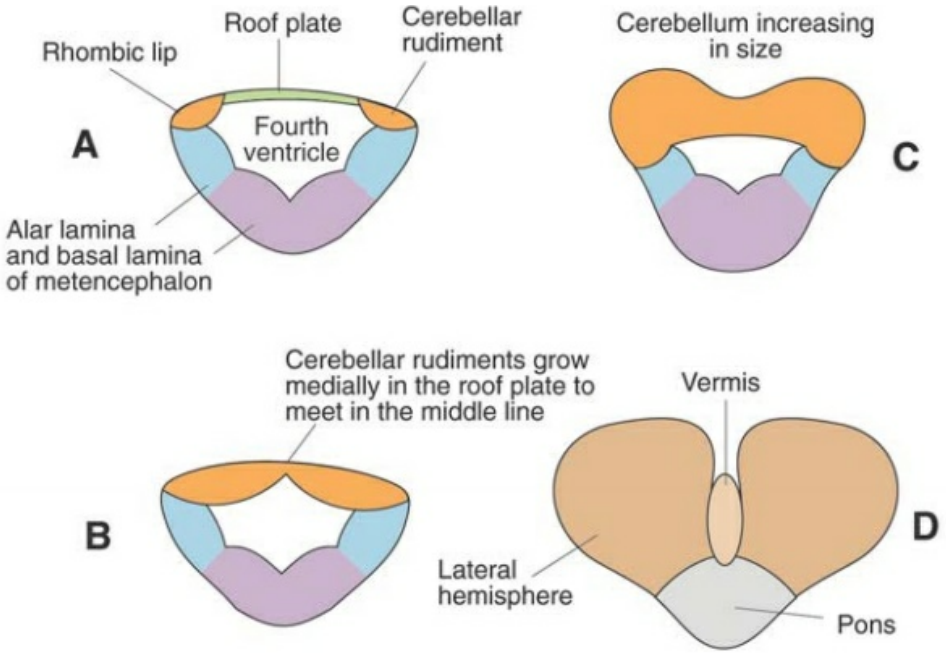
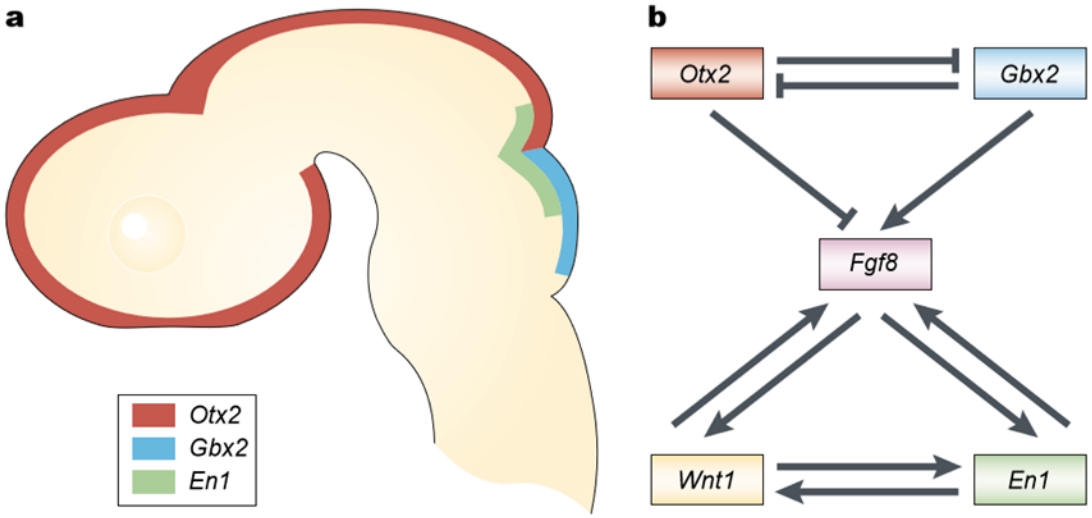


Fig. 7.5. Some stages in the development of the cerebellum. (A) Cerebellar rudiments appear from alar lamina of metencephalon. (B) They grow into the roof plate of the metencephalon to meet in the midline. (C) Cerebellum enlarges and bulges out of the fourth ventricle. (D) Lateral hemispheres and vermis can be distinguished.

Genetic control of the cerebellum

The cerebellumis derived fromdorsal rhombomere1, which comprises of the most anterior aspect of the hindbrain. Expression of the homebox genes Otx2 and Gbx2 anatagonise each other to establish the mid-brain-hindbrain boundary and the isthmic organizer.At embryonic day 2 Otx2 is expressed in the mesencephalon, and it is bounded posteriorly by the rostral metencephalon, whereas Gbx2 is expressed in the metencephalon and it is bounded anteriorly by the caudal mesencephalon. Otx2 negatively regulates Fgf8 expression where as Gbx2 maintains it The isthmic organizer is a signaling center that secretes fibroblast growth factor (8) a key molecule required for orchestrating multiple cerebellar development. The Fgf8 is a

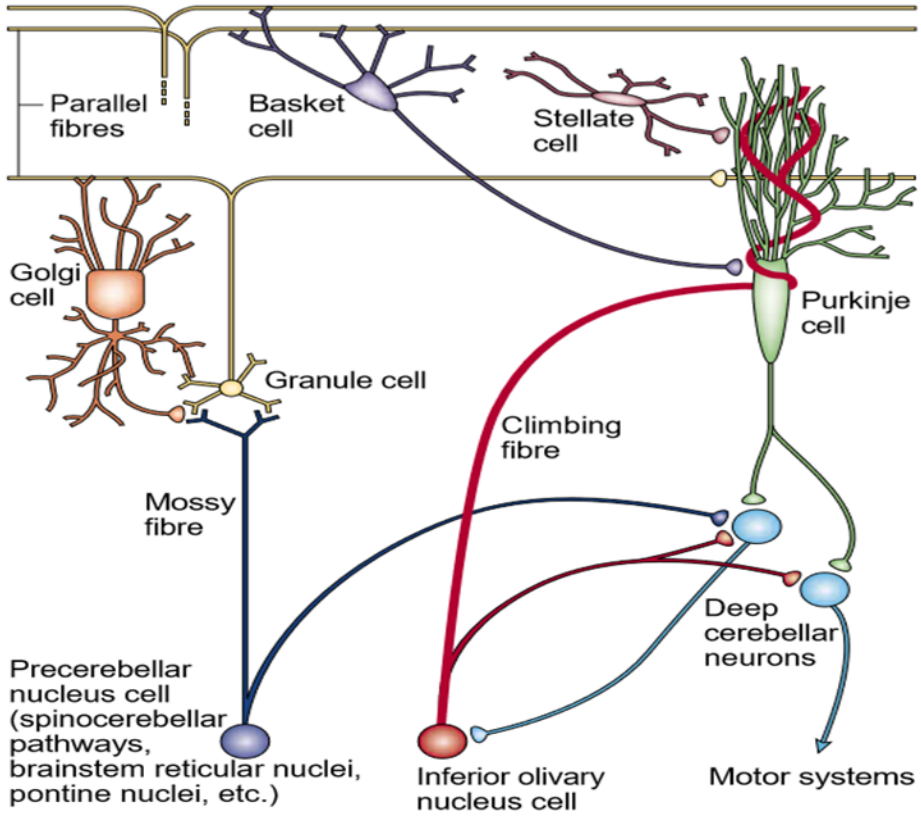
diffusible involved in regulating the various genes expressed in mid and hind brain region. Fgf8 exerts its action partially by inducing the expression of wingless homologue 1 (Wnt1) through Limhomebox 1b (Lmx1b). Wnt1, in turn, maintains the expression of Engrailed (En1), which then positively regulates Fgf8 expression, completing the feedback regulatory loop. Complete loss of FGF expression compromises isthmic organizer function and result in absence of the midbrain and cerebellum Transient Fgf8 expression during the initial stages of cerebellar development is sufficient to induce the formation of the lateral cerebellumbut not the vermis. Fgf8 cooperates with a number of well-characterized genes to control cerebellar development. Among these are the homebox genes engrailed1 (En1) and engrailed 2(En2)) and the paired box gene Pax2 and Pax5. Pax2 induces Fgf8 expression while En1 and En2 are necessary for its maintenances. Several other genes that are not part of this pathway are also important in patterning of the mid-/hindbrain region. Wnt1 and other patterning genes and together constitute another positive regulatory loop



Purkinje fiber,Rhombic limb and granule neurons

The external granular layer promotes Purkinje cell migration by secreting reelin (RELN), an extracellular matrix component attracting or repealing

precursors and axons during development, acting as an extracellular signaling molecule. Purkinje cells (PCs), Golgi neurons, stellate and basket cells all arise fromthe ventricular neuroepithelium PCs are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, PCs develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including Wnt3. Various growth factors are required for PC survival, including nerve growth factor, acetylcholine, neurotrophin 4/5, brain-derived neurotrophic factor and ciliary neurotrophic factor. 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 Purkinje cells begin to express the calcium-binding protein calbindin. Calbindin positive cells migrate

in a radial direction over the already formed deep cerebellar nuclei. These Purkinje cells then settle and become suspended beneath the external granular layer (EGL), awaiting the inward migration of granule neurons. The timely arrest of migration is dependent on the reelin pathway. Although Purkinje cells depend on signals from the granule neuron precursors to migrate, their differentiation programme seems to be independent of granule neurons. Math1, a transcription factor, is critical for the proper development of the granular layer of the cerebellum Mice deficient in Math1 show a loss of external granular layer. Purkinje cells develop extensive dendritic arbours and synapse onto granule neurons. Throughout the course of development, various growth factors are important for Purkinje cell survival. Nerve growth factor, acetylcholine, brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor have all been shown to have a positive effect on Purkinje cell number in vitro. Similarly, the Rorα (RAR-related orphan receptor α) gene is also important for the survival of Purkinje cells.

Table 1 | **Genes involved in various stages of cerebellar development**

Stages/areas of development	Genes, proteins and molecules
Cerebellar primordium	*Otx2, Gbx2, Fgf8, Wnt1, En1/2, Pax2/5,* Bmps, *Shh, Hoxa2*
Granule cell generation	*Math1, RU49/Zipro1, Zic1,2,3, Shh* pathway, *Ccnd2, p27, Neurod1, NSCL1*
Granule cell migration	Tag1, Tuj1, *Pax6,* Dcc/netrin pathway, *Unc5h2,3* GIRK2, astrotactin, thrombospondin, tenascin, neuregulin
Purkinje cell maintenance	Ngf, BDNF, ciliary neurotrophic factor, acetylcholine, Nt4/5, Rorα
Purkinje cell migration	Reelin pathway

Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip. The rhombic lip, located between the fourth ventricle and the metencephalic roof plate, gives rise to granule neurons. Proliferation in its germinal epitheliumis governed by the Math1 gene. Expression of the Math1 gene governs the germinal

epitheliumof the rhombic lip. Math1 is expressed in the mid-/hindbrain region and persists in the rhombic lip and many of its derivatives including the granule neurons of the cerebellumand the pontine nucleus of the precerebellar system The rhombic lip, granule neuron precursors proliferate and then assume a unipolar morphology, with a single process that projects away fromthe rhombic lip. Rhombic lip cells migrate to the cerebellar anlage and settle on its periphery to formthe 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 Shh pathway. As the cells continue to migrate, the external granular layer differentiates into outer and inner external granular layers (FIG. 4). Fromthe outer EGL, granule neuron precursors migrate into the inner EGL. In the inner EGL, granule neuron precursors no longer express Math1; instead, they express two other basic transcription factors, Neurod1 and NSCL1. Neurod1 is important for the survival of inner EGL granule neuron precursors. The next stage of development for granule neuron precursors is the inward migration into the inner granule layer (IGL) under the guidance of radial glial fibres. The final stage of granule neuron maturation occurs after precursor cell migration into the inner granule layer.

Cyclin D2 is important in cerebellar granule neuron proliferation and in the final maturation of granule neurons the gene Wnt7a

Neurodevelopmental disorders

Cerebellar malformation are increasingly recognized in the fetal period and they include

1. Joubert syndrome: The disorder presents 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 (they are cell surface microtubule-based organelles that dynamically extend fromcells to receive and process molecular and mechanical signaling cues). Interestingly, primary cilia are determinant for sonic hedgehog signal transduction. Disruption of primary cilia formation blocks the proliferation of neural progenitors of granule cells mediated by sonic hedgehog.

2. Rhombencephalosynapsis: associated with learning disabilities, a malformation of the hindbrain characterized by fusion of the cerebellar hemisphere and denate nuclei. It is assumed that the disorder is due to a failure of dorsal patterning at the mid-brain boundaries
3. Autismspectrumdisorders are characterized 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 cerebellumof austic patients. IL-6 impacts upon developmentof the cerebellum,impairs neural cell adhesion, migration and causing an excessive formation of excitatory synapses
4. 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.

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