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**ASSIGNMENT QUESTION:** Write a concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorders.

**THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM**

The cerebellum (‘little brain’) resides at the anterior end of the hindbrain and is classically defined by its role in sensory-motor processing. 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.

The major features of cerebellar development can be briefly summarized as follows. Neuronal populations are generated in a sequential manner. The inhibitory interneurons emerge from the ventricular zone and the glutamatergic neurons are generated by the rhombic lip. In mouse, the glutamatergic and gabaergic neurons in nuclei are produced first, followed by Purkinje neurons. It is established that gabaergic interneurons of the cerebellar cortex originate from a ventricular zone progenitor. After generation of cerebellar nuclei, the external granular layer is formed from precursors of granule cells originating from the rhombic lip. Granule cells will migrate to form the internal granular layer. Survival and maintenance of Purkine neurons and granule cells is dependent on the antiapoptotic protein Lifeguard, which is highly expressed in the cerebellum and is strongly upregulated during postnatal brain development. Lifeguard antagonizes the FAS pathway. FAS receptors tune neuronal survival following trophic factors deprivation. Lifeguard affects cerebellar size, internal granular layer thickness, and Purkinje cell development, suggesting that lifeguard could participate in the pathogenesis of various human cerebellar disorders characterized by cerebellar atrophy. Glutamatergic unipolar brush cells migrate to the internal granular layer. Whereas the ventricular zone will lose its progenitors at late embryogenic stages, the rhombic lip remains active until postnatal period.

The relationship between circulating hormones and cerebellar development is well demonstrated. In particular, thyroid hormone plays a critical role in brain development. The thyroid hormone receptor is a ligand-regulated transcription factor binding to a specific DNA sequence called thyroid-hormone-responsive element. The receptor recruits various coregulators such as coactivator and corepressor in a ligand-dependent manner to modulate the transcription of target genes. It may also interact with other nuclear receptors such as Rora (retinoic-acid-related orphan receptor alpha; see below) whose expression is regulated by the thyroid hormone during the first postnatal two weeks.

In perinatal hypothyroidism, the growth and branching of Purkinje cell dendrites are greatly reduced, there is a reduction of synapses between granule cells and Purkinje neurons, migration of granule cells to the internal granule cell layer is delayed and synaptic connectivity within the cerebellar cortex is deficient. Thyroid deficient rats show a persistence of synaptic sites of climbing fibers for a longer time (see section on the remodeling of the olivocerebellar projection) along with an underdevelopment of cerebellar glomeruli. Performance of the hypothyroid animals is impaired in tests of adaptive behavior.

In the hypothyroid cerebellum (right panel), disappearance of the external granular layer is delayed consequently to the retarded proliferation and migration of granule cells to the internal granular cell layer. The arborisation of the dendrites of Purkinje neurons (P) is decreased. The connectivity between parallel fibers and Purkinje cells is reduced. The synaptic connections between mossy fibers and granule cells are decreased as compared to the euthyroid condition. Green open circles: climbing fibers synapses. The discovery that Purkinje neurons possess steroidogenic enzymes and produce progesterone from cholesterol in the neonatal period has provided a link between steroidogenesis and development of cerebellar circuits. Concentrations of progesterone and allopregnenolone are high in the cerebellum during the post-natal life. Formation of cerebellar circuitry is dependent on a local steroidogenesis, acting through neurotrophic factors such as BDNF . This emphasizes a potential novel bridge between neurosteroidogenesis and motor learning, with possible therapeutical implications in developmental disorders.

**The Engrailed-2 Gene**

The engrailed (En) homeobox 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 fiber systems to subsets of cerebellar lobules, showing a main role for the afferent topography in the cerebellar circuitry. Initially, the En1/2 mRNA/protein are expressed in the ventricular zone. During early post-natal cerebellogenesis, En1/2 are expressed in spatially restricted patterns in most cell types.

**Math1**

The specification and differentiation of glutamatergic lineages is dependent upon Math1, a transcription factor of the bHLH class. Math1 is critical for the proper development of the granular layer of the cerebellum. Mice deficient in Math1 show a loss of glutamatergic neurons in cerebellar nuclei, a loss of external granular layer and unipolar brush cells. In addition, Math1 null embryos lack interneurons giving rise to the spinocerebellar and cuneocerebellar tracts

**Ptf1a and Ascl1**

Cerebelless mutants have a deficit in the transcription factor Ptf1a (pancreatic transcription factor 1a). They show a lack of Purkinje cells and gabaergic interneurons. It has been demonstrated that climbing fiber neurons are derived from the Ptf1a domain. In Ptf1a null mutants, immature climbing fiber neurons cannot migrate or differentiate, causing a failure in the formation of the inferior olivary nucleus. Ptf1a is also involved in the control of fate and survival of neurons during development. In human, mutations of Ptf1a are associated with cerebellar agenesis

**Rora (Retinoic-Acid-Related Orphan Receptor Alpha) Gene**

Rora is a transcription factor encoding a retinoid-like nuclear receptor which is highly expressed in the cerebellum. Rora belongs to the steroid-thyroid hormone receptor superfamily. Its endogenous ligand is cholesterol which is abundantly present in each cell. Therefore, Rora acts as if it is a constitutively active nuclear receptor. It was initially thought that Rora was exclusively expressed in neurons, but recent data show that it is also expressed in glial cells especially in astrocytes. Rora plays a pivotal role in the development of the cerebellum. However, its functions extend beyond development. For instance, Rora also protects neurons against oxidative stress and shows an anti-inflammatory action by inhibiting the NF-Kappa-B pathway. The autosomal recessive *staggerer* mutation is associated with a severe degeneration of Purkinje neurons with a nearly total absence of granule cells at the end of the first postnatal month.

**Reelin and Cerebellar Development**

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. Reelin deficient mice (Reeler) show a severe cerebellar hypoplasia. They exhibit Purkinje cell migration defects and cerebellar nuclei are impaired. Foliation is absent. Reelin continues exerting activities beyond birth. It modulates long-term potentiation and is thus involved in learning. In the adult brain, Reelin regulates structural and functional properties of synapses.

**Sonic Hedgehog and Cerebellar Development**

Sonic hedgehog is highly expressed in the cerebellum. Sonic hedgehog is a morphogenetic factor which is a masterplayer in cerebellar patterning and foliation. Indeed, sonic hedgehog controls the proliferation of progenitors in the cerebellum. Sonic hedgehog pathway involves the GLI family of transcription factors. The binding of sonic hedgehog to the transmembrane receptor Patched 1 triggers a cascade of events tuning cAMP production. A link between cholesterol metabolism, sonic hedgehog and cerebellar development has been established. Indeed, cholesterol deficiencies are associated with defects in the sonic hedgehog signaling (cholesterol is an activator of sonic hedgehog) and cause cerebellar malformations. While deletion of sonic hedgehog leads to an absence of foliation and underdevelopment of the cerebellum, the sonic hedgehog mutants show a larger cerebellum, even with an extra-lobule, demonstrating how sonic hedgehog determines cerebellar morphology and shape. Cyclins D1 and D2 are transcriptional targets of sonic hedgehog. Delection of cyclin D2 is associated with a mild hypoplastic cerebellum.

Sonic hedgehog pathway is also controlled by negative regulators, such as PACAP (pituitary adenylate-cyclase activating polypeptide). Knock-out mice for PACAP show an overactive sonic hedgehog pathway with enlargement of the external granular layer. Sonic hedgehog is also deactivated by FGF-2, which triggers the differentiation of neural precursors of granule cells.

Sonic hedgehog is implicated in the formation of medulloblastoma, an aggressive tumor of the cerebellum. Development of sonic hedgehog antagonists might be considered to manage this tumor.

**NEURODEVELOPMENTAL DISORDERS**

* **Ataxia with oculomotor apraxia**

Ataxia with oculomotor apraxia is a condition characterized by problems with movement that worsen over time. The hallmark of this condition is poor coordination and balance (ataxia), which is often the first symptom. Most affected people also have oculomotor apraxia, which makes it difficult to move their eyes side-to-side. People with oculomotor apraxia have to turn their head to see things in their side (peripheral) vision.

Mutations in the [APTX](https://ghr.nlm.nih.gov/gene/APTX), [SETX](https://ghr.nlm.nih.gov/gene/SETX), or [PNKP](https://ghr.nlm.nih.gov/gene/PNKP) gene cause ataxia with oculomotor apraxia types 1, 2, or 4, respectively. Mutations in another gene cause ataxia with oculomotor apraxia type 3.

The APTX, SETX, and PNKP genes provide instructions for making proteins that are involved in repairing damaged DNA. Mutations in any of these genes reduce the amount of functional protein produced from that gene. This shortage prevents the efficient repair of DNA damage, which leads to the accumulation of broken DNA strands. DNA breaks may be caused by potentially harmful molecules (called reactive oxygen species) produced during normal cellular functions, natural and medical radiation, or other environmental exposures. They may also occur when chromosomes exchange genetic material in preparation for [cell division](https://ghr.nlm.nih.gov/art/large/mitosismeiosis.jpeg). DNA damage that is not repaired makes the cell unstable and can lead to cell death. It is thought that cell death has a particularly severe effect in the brain because the nervous system does not replace nerve cells that have been lost. The part of the brain involved in coordinating movements (the cerebellum) is especially at risk. It is thought that the loss of brain cells in the cerebellum causes the movement problems characteristic of ataxia with oculomotor apraxia.

* **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 peduncles which are more horizontally oriented and hypoplastic cerebellar vermis) is very suggestive. Joubert syndrome is associated with mutations of genes encoding components of the primary cilia. 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

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