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

The mature cerebellum has exquisite, stereotypical morphology, foliation, and lamination, which are consistent between individuals and highly conserved across vertebrates. At the cellular level, unlike other regions of the CNS, the cerebellum is composed of very few neuronal types, each with distinct morphology, arranged in discrete lamina, and connected in stereotypical circuits. The cerebellum has essential roles in motor coordination, but is not essential for viability. Thus, compared with other regions of the central nervous system (CNS) the cerebellum has been more amenable to genetic studies since disruptions in development, which lead to abnormal morphology or function, are readily observed in obvious neurological and behavioral phenotypes. Because of this, it has been possible to obtain a precise understanding of cerebellar development. The mechanisms deciphered from the study of cerebellar development have broad applicability to other CNS regions such as the cerebral cortex. For example, while initial insights regarding the function of the Reelin gene were gleaned from studying the cerebella of reeler mice, recent studies have revealed that this gene is required for the emigration of dentate gyrus progenitors from a transient subpial zone and into the subgranular zone. Also, while Foxc1 controls normal cerebellar and posterior fossa development by regulating secreted growth factor signals from the mesenchyme, it is also required for the development of meningeal structures that in turn influence skull and cortical development.

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 (Carletti and Rossi, 2008). 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 (Leto and Rossi, 2011). 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. It is interesting to note that these events occur at the third trimester of development in human. Survival and maintenance of Purkinje 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 (Hurtado de Mendoza et al., 2011). Lifeguard antagonizes the FAS pathway. FAS receptors tune neuronal survival following trophic factors deprivation (Raoul et al., 2000). 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 Engrailed-2 Gene

The engrailed (En) homeobox transcription factor family is critical for the patterning of cerebellar lobules and for Purkinje cells protein stripes (Kuemerle et al., 1997). 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 (Sillitoe et al., 2010). 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. It is plausible that En1/2 are implicated in neurodevelopmental disorders such as autism spectrum disorder. Indeed, mutant mice EN2−/− show neurobehavioral and neurochemical deficits suggestive of autism spectrum disorder (Cheh et al., 2006).

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 (Bermingham et al., 2001).

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 (Yamada et al., 2007). 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 (Sellick et al., 2004).

Ascl1 directs ventricular neuroepithelium progenitors toward inhibitory interneuron fate and suppresses the astrocytic differentiation (Grimaldi et al., 2009). Mice lacking Ascl1 in the cerebellum exhibit a major decrease of cerebellar interneurons and an imbalance between oligodendrocytes and astrocytes (Sudarov et al., 2011).

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 (Hamilton et al., 1996). Rora belongs to the steroid-thyroid hormone receptor superfamily (Koibuchi, 2008). Its endogenous ligand is cholesterol which is abundantly present in each cell. Therefore, Rora acts as if it is a constitutively active nuclear receptor (Koibuchi, 2008). 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 (Journiac et al., 2009). Rora plays a pivotal role in the development of the cerebellum, olfactory bulb, and retina (Jetten, 2009). 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 (Delerive et al., 2001; Boukhtouche et al., 2006).

Mutations of Herc Gene

Proteins with HECT domains act as ubiquitin ligases. Recently, it has been shown that mutations in the highly conserved N-terminal RCC1-like domain of the HERC1 protein cause a progressive Purkinje cell loss leading to severe ataxia with reduced growth and lifespan in homozygous mice aged over two months (tambaleante mutant mice; Mashimo et al., 2009). Activities of the proteins encoded by the HERC gene family are critical in a number of important cellular processes such as cell cycle, cell signaling, and membrane trafficking. It is now established that they play a key contribution in the physiology of Purkinje neurons.

**Genetic Bases of Known Cerebellar Disorders**

* 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 (Beffert et al., 2004). In the adult brain, Reelin regulates structural and functional properties of synapses. Its overexpression may increase markedly the long-term potentiation responses and it has been proposed that Reelin controls developmental processes remaining active in the adult brain (Pujadas et al., 2010). In human, reelin might be implicated in some forms of lissencephaly (due to neuronal migration defect) and could contribute to the pathogenesis of autism.
* 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 (Landis and Sidman, 1978). The homozygous mouse Rorasg/Rarasg is highly ataxic, whereas the heterozygous mouse Rora+/Rarasg appears phenotypically normal, showing disabilities during challenging tasks.
* 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 (Sellick et al., 2004). Mice lacking Ascl1 in the cerebellum exhibit a major decrease of cerebellar interneurons and an imbalance between oligodendrocytes and astrocytes (Sudarov et al., 2011).
* Ten genes have been identified that cause Joubert syndrome. A mutation in the AHI1 (JBTS3) gene is responsible for this condition in approximately 11% of families. Affected individuals with this gene mutation often have impaired vision due to retinal dystrophy. A mutation in the NPHP1 (JBTS4) gene causes approximately 1-2% of Joubert syndrome. Affected individuals with this gene mutation often develop a progressive kidney disease called nephronophthisis. A mutation in the CEP290 (JBTS5) gene causes about 4-10% of Joubert syndrome. Mutations in the TMEM67 (JBTS6), JBTS1, JBTS2, JBTS7, JBTS8 and JBTS9 genes are also associated with Joubert syndrome. Other genes responsible for this condition are currently unknown.
* It is plausible that En1/2 are implicated in neurodevelopmental disorders such as autism spectrum disorder. Indeed, mutant mice EN2−/− show neurobehavioral and neurochemical deficits suggestive of autism spectrum disorder (Cheh et al., 2006).

References

* Frontiers in neuroanatomy
* NCBI, OMC US National Library of Medicine National Institutes of Health