NEUROANATOMY ASSIGNMENT

CEREBELLUM AND ITS CONNECTIONS

AMOO OLUWANIFEMI MICHAEL

18/MHS01/379

300 LEVEL

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

**STRUCTURE OF THE CEREBELLUM**

The cerebellum of mammals and birds can be divided into a reproducible series of anteroposterior folds called lobules. Lobule architecture is distinct between anatomical divisions that separate the mediolateral axis of the cerebellum into three broad regions. The most medial region is called the vermis, which is surrounded on either side by the Para vermis. Even more laterally are the hemispheres, which in mice are each roughly the same size as the vermis. The paraflocculi and flocculi are lateral extensions of the hemispheres that extend outward and curl toward the underside of the cerebellum. None of these anatomical divisions are present when the cerebellum first forms. The transformation of the initially smooth embryonic cerebellum into complex lobules and mediolateral regions occurs through a series of dramatic cellular movements that are largely complete by ∼postnatal day. The cellular makeup of the cerebellum is well understood. Each mediolateral region of the cerebellum generally contains all of the major cell types where they are organized around a repeated anatomical plan. This plan consists of a three-layered cortex that surrounds an inner core of white matter and the cerebellar nuclei. The innermost layer is called the granular layer, which is dominated by the small granule cells (the most numerous type of neuron in the brain), but also includes mossy fiber terminals, Golgi cells, Lugaro cells, and unipolar brush cells (UBCs). The outermost layer is the molecular layer, which contains granule cell axons (parallel fibers), climbing fiber terminals, Purkinje cell dendrites, stellate cells, and basket cells. Between these two layers is a monolayer of Purkinje cell somata that make up the Purkinje cell layer. Sandwiched between the Purkinje cells are specialized glial cells called Bergmann glia, and in lower numbers candelabrum cells. In addition to climbing and mossy fibers, a third class of afferents that have ‘beaded’ protrusions16 and are presumed to be neuromodulatory, terminate in all three layers of the cerebellum and within the cerebellar nuclei.

**ESTABLISHMENT OF THE CEREBELLAR PRIMORDIUM**

The cerebellum is derived from dorsal rhombomere, which comprises the most anterior aspect of the hindbrain. Expression of the homeobox genes Otx2 and Gbx2 are essential for the development of the midbrain and hindbrain. During development, these two genes are expressed in abutting domains where they antagonize each other to establish the mid/hindbrain boundary and formation of an isthmic organizer (IsO). The IsO functions as a classic signaling center by secreting fibroblast growth factor 8 (FGF8), which maintains the posterior border of Otx2 expression and is crucial for normal cerebellar development. FGF expression is strongly controlled during hindbrain development and its loss results in the absence of the midbrain and cerebellum. Accordingly, FGF expression is required for cell survival and to regulate gene expression in the mid/hindbrain region. Different mediolateral and anteroposterior regions of the midbrain and cerebellum require varying levels and durations of FGF signaling for proper development. For instance, a slight reduction in FGF8 signaling results in a specific loss of posterior midbrain and the vermis. Moreover, the different isoforms of FGF8 that are expressed in the IsO have specific receptor affinities and their ectopic expression causes distinct developmental disruptions with mis-expression of FGF8b causing a deletion of the midbrain and gain of cerebellar territory whereas FGF8 promotes an increase in midbrain tissue.

**MIGRATION OF CEREBELLAR PROJECTION NEURONS**

In mice, glutamatergic cells of the cerebellar nuclei are the first cells to become post-mitotic between ∼E10 and E12, followed closely by Purkinje cells between ∼E10 and E13. The glutamatergic cerebellar nuclei migrate away from the rhombic lip tangentially over the cortical surface, and once they reach the anterodorsal aspect of the cerebellum they cluster in the nuclear transitory zone (NTZ). All Purkinje cells have left the ventricular zone by late E13 and apparently migrate along radial glia into symmetrical clusters that are detected by gene expression starting at ∼E14 in mice. The decision of a Purkinje cell to incorporate into a specific cluster seems to be determined by its birth date. Purkinje cell clusters are multilayered and situated between migrating cerebellar nuclei cells. In the mature cerebellum, Purkinje cells are no longer clustered but instead are organized into a monolayer that is established by ∼P4/5 in rodents.12 Proper Purkinje cell migration is dependent on the presence of the extracellular matrix protein reelin and its downstream effector molecules. The migration of Purkinje cells apparently occurs simultaneously with their axon genesis as Purkinje cell axons have been observed in their target locations by ∼E14.

**ESTABLISHING CONNECTIONS TO THE CEREBELLUM**

Mossy fibers contact granule cells and UBCs in the adult cerebellum but transiently contact Purkinje cells during late embryonic and early postnatal development. Although it remains a mystery as to how these transient contacts support cell-to-cell communication, there is some evidence that they do form electrically active connections even during early postnatal stages. Thereafter, the transient connections are severed, perhaps mediated by BMP4 signaling, and mature synaptic contacts are established. Current theory suggests that through transient interactions Purkinje cells may instruct other developing cerebellar neurons to take residence within specific functional circuits. Mossy fiber patterns resolve into clear mediolateral bands during the first postnatal week, just prior to when individual fibers translocate from Purkinje cells to synapse upon granule cells. The refinement of parasagittal boundaries in the afferent map may require the activity of granule cells, as in vivo infusion of granule-cell activity blockers resulted in mossy fiber bands with poorly defined boundaries. Therefore, although the general topographic plan may be driven by Purkinje cell gene function, the refinement of the map (and perhaps also its maintenance) into structurally and functionally precise longitudinal zone connections instead might depend on active granule cell contacts. In the mature cerebellum, inferior olive axons split into an average of six to seven climbing fibers that synapse upon Purkinje cells in the same sagittal. The end result of this configuration is that each Purkinje cell receives input from only a single climbing fiber, which ‘climbs’ to the dendrites of the Purkinje cell. However, during development Purkinje cells are initially contacted somatically by several climbing fibers, which are eventually pruned away to achieve the one-to-one relationship. Climbing fiber pruning can be considered as a two-part process: the first of which is independent of granule cell–Purkinje cell signaling, while the second is dependent upon the activity between parallel fibers and Purkinje cells. The mechanisms controlling each phase may be teased apart by analyzing the defects in naturally occurring mutant mice that lack proper granule cell–Purkinje cell interactions but exhibit normal climbing fiber regression in the early postnatal period. One group has provided electrophysiological evidence that the ability of a climbing fiber to induce large calcium influxes may lead to its status as the ‘winning’ fiber before parallel fiber activity is involved. However, parallel fiber activity was shown to be crucial for the late stage of pruning, which occurs from ∼P10

**CONCLUSION**

Purkinje cells interact and cooperate with the other cerebellar cell types to regulate multiple developmental processes including the formation of functional topographic zones. In addition to Purkinje cell patterning, the development of zonal circuits requires the proper targeting of afferent fibers, settling of interneurons into specific positions, and the restriction of dendrites to sagittal boundaries. Not surprisingly, physical and genetic insults to the cerebellum result in a pattern of Purkinje cell death that respects the fundamental zonal architecture. Cerebellar longitudinal zones comprise specific neural connections that facilitate behaviorally relevant functions. Accordingly, the synaptic activity that apparently underlies cerebellar motor learning may be restricted by zonal boundaries. One intriguing question about cerebellar zones is how are these complex units of communication formed during development? In accordance with the idea that gene function and neural activity transform embryonic patterns into a precise functional map in the adult cerebellum, Watt et al recently demonstrated in an elegant study that early postnatal Purkinje cells are linked by axon collaterals that propagate traveling waves of activity in the sagittal plane. It was suggested that these compartmentalized activity waves might play a critical role in shaping circuit connections during the formation of functional maps. Altogether, these data strongly suggest that longitudinal zones are a fundamental unit of the developing and adult cerebellum, and here we highlight that their formation provides a powerful inroad into understanding how complex circuits are established.

**CEREBELLAR DISORDERS AND ITS GENETIC BASES**

1. **HUNTINGTON DISEASE**

Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin

Genetic Bases: Mutations in the HTT gene cause Huntington disease. The HTT gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain. The HTT mutation that causes Huntington disease involves a DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. In people with Huntington disease, the CAG segment is repeated 36 to more than 120 times. People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of Huntington disease, while people with 40 or more repeats almost always develop the disorder. An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington disease.

1. **ATAXIA-TELANGIECTASIA**

Ataxia-telangiectasia is a rare inherited disorder that affects the nervous system, immune system, and other body systems. This disorder is characterized by progressive difficulty with coordinating movements (ataxia) beginning in early childhood, usually before age 5. Affected children typically develop difficulty walking, problems with balance and hand coordination, involuntary jerking movements (chorea), muscle twitches (myoclonus), and disturbances in nerve function (neuropathy). The movement problems typically cause people to require wheelchair assistance by adolescence. People with this disorder also have slurred speech and trouble moving their eyes to look side-to-side (oculomotor apraxia). Small clusters of enlarged blood vessels called telangiectasia, which occur in the eyes and on the surface of the skin, are also characteristic of this condition. Affected individuals tend to have high amounts of a protein called alphafetoprotein (AFP) in their blood. The level of this protein is normally increased in the bloodstream of pregnant women, but it is unknown why individuals with ataxiatelangiectasia have elevated AFP or what effects it has in these individuals. People with ataxia-telangiectasia often have a weakened immune system, and many develop chronic lung infections. They also have an increased risk of developing cancer, particularly cancer of blood-forming cells (leukemia) and cancer of immune system cells (lymphoma). Affected individuals are very sensitive to the effects of radiation exposure, including medical x-rays. The life expectancy of people with ataxiatelangiectasia varies greatly, but affected individuals typically live into early adulthood.

Genetic Bases: Mutations in the ATM gene cause ataxiatelangiectasia. The ATM gene provides instructions for making a protein that helps control cell division and is involved in DNA repair. This protein plays an important role in the normal development and activity of several body systems, including the nervous system and immune system. The ATM protein assists cells in recognizing damaged or broken DNA strands and coordinates DNA repair by activating enzymes that the broken strands. Efficient repair of damaged DNA strands helps maintain the stability of the cell's genetic information. Mutations in the ATM gene reduce or eliminate the function of the ATM protein. Without this protein, cells become unstable and die. Cells in the part of the brain involved in coordinating movements (the cerebellum) are particularly affected by loss of the ATM protein. The loss of these brain cells causes some of the movement problems characteristic of ataxiatelangiectasia. Mutations in the ATM gene also prevent cells from responding correctly to DNA damage, which allows breaks in DNA strands to accumulate and can lead to the formation of cancerous tumors.

1. **JOUBERT SYNDROME**

Joubert syndrome is a disorder that affects many parts of the body. The signs and symptoms of this condition vary among affected individuals, even among members of the same family. The hallmark feature of Joubert syndrome is a combination of brain abnormalities that together are known as the molar tooth sign, which can be seen on brain imaging studies such as magnetic resonance imaging (MRI). This sign results from the abnormal development of structures near the back of the brain, including the cerebellar vermis and the brainstem. The molar tooth sign got its name because the characteristic brain abnormalities resemble the cross-section of a molar tooth when seen on an MRI. Most infants with Joubert syndrome have low muscle tone (hypotonic) in infancy, which contributes to difficulty coordinating movements (ataxia) in early childhood. Other characteristic features of the condition include episodes of unusually fast (hyperpnea) or slow (apnea) breathing in infancy, and abnormal eye movements (ocular motor apraxia). Most affected individuals have delayed development and intellectual disability, which can range from mild to severe. Distinctive facial features can also occur in Joubert syndrome; these include a broad forehead, arched eyebrows, droopy eyelids (ptosis), widely spaced eyes (hypertelorism), lowest ears, and a triangle-shaped mouth. Joubert syndrome can include a broad range of additional signs and symptoms. The condition is sometimes associated with other eye abnormalities (such as retinal dystrophy, which can cause vision loss, and coloboma, which is a gap or split in a structure of the eye), kidney disease (including polycystic kidney disease and nephron phthisis), liver disease, skeletal abnormalities (such as the presence of extra fingers and toes), or hormone (endocrine) problems. A combination of the characteristic features of Joubert syndrome and one or more of these additional signs and symptoms once characterized several separate disorders. Together, those disorders were referred to as Joubert syndrome and related disorders (JSRD). Now, however, any instances that involve the molar tooth sign, including those with these additional signs and symptoms, are usually considered Joubert syndrome.

Genetic Bases: Joubert syndrome typically has an autosomal recessive pattern of inheritance, which means both copies of a gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they usually do not show signs and symptoms of the condition. Rare cases of Joubert syndrome are inherited in an X-linked recessive pattern. In these cases, the causative gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass x Linked traits to their sons.

© 2012 Wiley Periodical s, Inc.