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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 cerebellum represents 10% of the brains total volume, but contains more than half of our neurons. It acts as a coordination centre, using sensory inputs from the periphery to achieve our movement and balance. It is one of the first structures in the brain to begin to differentiate, but one of the last to mature, and its cellular organization continues to change for many months after birth. In humans, the cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip. Two primary germinal zones generate the cells that make up the cerebellum. Each 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 including transformation of the smooth cerebellar surface into an intricately patterned series of folds, formation of three distinct cellular layers, and the demarcation of parasagittal gene expression domains. Together, these structural and molecular organizations are thought to support the proper connectivity between incoming afferent projections and their target cells. After birth, genetic programs and neural activity repattern synaptic connections into topographic neural networks called modules, which are organized around a longitudinal zone plan and are defined by their molecular, anatomic, and functional properties. Soon after the cerebellar primordium is formed at the midbrain/hindbrain boundary, two primary germinal zones, the ventricular zone and the rhombic lip, sequentially generate various inhibitory and excitatory neurons, respectively. While the migration of cerebellar neurons extends well into postnatal development, work in rodents demonstrates that embryonic Purkinje cells settle into molecularly distinct parasagittal ‘clusters’, which appear to serve as a template around which circuit architecture is built. The mature circuitry of the cerebellum is organized into functional longitudinal zones. In addition to their unique circuit connectivity, Purkinje cell zones are marked by parasagittal stripes of gene and protein expression, the adult correlates of embryonic clusters. Parasagittal molecular domains are maintained even when the cerebellar surface exhibits very rapid and extensive growth along its anteroposterior axis during the stereotyped folding process called foliation. Afferent fibers arrive in the cerebellum during late embryonic and early postnatal development and terminate within specific folds in a crude map that reflects a positional code defined by Purkinje cell lineages and gene expression. Then, activity dependent mechanisms fine-tune afferent termination domains by allowing individual connections to be integrated seamlessly into longitudinal zones that can be identified by specific Purkinje cell stripes and are innervated by distinct subsets of afferent projections. The proper functioning of the cerebellum therefore requires an elaborate interplay between genetic- and activity-dependent mechanisms to guide its morphogenesis and establish its circuit connections.

ESTABLISHMENT OF CEREBELLAR PRIMODIUM:

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 FGF8a promotes an increase in midbrain tissue. The ability of FGF8 to induce distinct structures depends not only on the strength of the signal but also on its duration. For example, transient Fgf8 expression between E8.5 and E10 is sufficient to induce the formation of the lateral cerebellum but not the vermis. A number of other genes cooperate with Fgf8 to control cerebellar development. Among these are the homeobox genes engrailed 1 (En1) and engrailed 2 (En2), and the paired box genes Pax2 and Pax5. Pax2 induces Fgf8 expression while En1 and En2 are necessary for its maintenance. Interestingly, notch signaling may be upstream of all the above-mentioned genes during the establishment of the IsO. Although a great deal of attention has been given to Fgf8, other members of the Fgf family are also crucial for cerebellar development (e.g., Fgf17 and Fgf1848) and several of the mRNAs that encode FGF signaling molecules exhibit a patterned expression postnatally.

DEVELOPMENT AND ORGANIZATION OF CEREBELLAR STRIPPED GENE EXPRESSION:

The molecular heterogeneity of Purkinje cells is obvious from ∼E1497 in mice. However, because the expression of Purkinje cell markers is temporally dynamic and because their patterns can be different at each stage, they can be divided into early markers that demarcate embryonic clusters, late markers that define adult stripes, and markers that are constitutively expressed and bridge between the clusters and stripes. The temporal segregation of Purkinje cell stripe markers highlights an interesting phase during the second and third weeks of life. Most well-known molecular markers either stop being expressed in stripes or begin being expressed in stripes during this period. This temporal gap in stripe patterns raised the question of whether cellular and/or molecular information link early and late cerebellar patterning. Several studies have now demonstrated a lineage relationship between clusters and stripes. The general message echoed by these studies is that gene expression patterns in Purkinje cell clusters are repatterned into adult stripes and individual embryonic clusters seem to contribute to multiple adult stripes. However, how the cluster to stripe transformation takes place is poorly understood and the molecular signals that mediate it are not known (although reelin signaling and patterned developmental cell death of Purkinje cells may be involved). One pressing issue in the field has been to identify the genetic programs that instruct the formation of Purkinje cell stripes. At least two families of transcription factors have been implicated: the atypical helix loop-helix transcription factor early B-cell factor 2 (EBF2) and the homeodomain transcription factors EN1/2. A landmark study by Croci et al. demonstrated that Ebf2 controls the fate of ALDOC positive versus ALDOC negative Purkinje cells. In the adult mouse cerebellum, Ebf2 expression is restricted to ALDOC negative Purkinje cells. Removal of Ebf2 results in a subset of ALDOC negative Purkinje cells expressing ALDOC positive markers in addition to the normal ALDOC negative ones. These results suggest that EBF2 is a repressor of the ALDOC positive Purkinje cell phenotype. En1/2 are expressed in stripes from ∼E15 to postnatal stages of cerebellar development. It is now well established that En1 and En2 also play critical roles in patterning striped gene expression. Interestingly, while En1 is dominant in patterning stripes in lobules I–V and VIII/IX, En2 is dominant in generating the stripe patterns in lobules VI/VII and IX/X. Although the role of ALDOC in stripes has not been determined, the temporal relationship between stripe patterning and synaptogenesis suggests that late onset stripes may be tightly linked to circuit function. We speculate that blocking ALDOC stripe formation could contribute to the motor defects observed in mice with zonal alterations.

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 plane. 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 and onward.

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 behaviourally 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.147 recently demonstrated in an elegant study that early postnatal Purkinje cells are linked by axon collaterals that propagate travelling 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.

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CEREBELLAR DISORDER:

1. Ataxia-Talangiectasia: 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 telangiectases, 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 ataxia telangiectasia 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 and cancer of immune system cell. Affected individuals are very sensitive to the effects of radiation exposure, including medical x-rays. The life expectancy of people with ataxia telangiectasia varies greatly, but affected individuals typically live into early adulthood.

CAUSES:

Mutation in the ATM gene causes ataxia telangiectasia. 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 fix 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 are particularly affected by loss of the ATM protein. The loss of these brain cells causes some of the movement problems characteristic of ataxia telangiectasia. 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 (hypotonia) 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 broad forehead, arched eyebrows, droopy eyelids, widely spaced eyes, low set ears and triangular 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 nephronophthisis), 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.

CAUSES:

Joubert syndrome can be caused by mutations in more than 30 genes. The proteins produced from these genes are known or suspected to play roles in cell structures called primary cilia. Primary cilia are microscopic, Finger-like projections that stick out from the surface of cells and are involved in sensing the physical environment and in chemical signaling. Primary cilia are important for the structure and function of many types of cells, including brain cells (neurons) and certain cells in the kidneys and liver. Primary cilia are also necessary for the perception of sensory input, which is interpreted by the brain for sight, hearing, and smell. Mutations in the genes associated with Joubert syndrome lead to problems with the structure and function of primary cilia. Defects in these cell structures can disrupt important chemical signaling pathways during development. Although researchers believe that defective primary cilia are responsible for most of the features of these disorders, it is not completely understood how they lead to specific developmental abnormalities. Mutations in the genes known to be associated with Joubert syndrome account for about 60 to 90 percent of all cases of this condition. In the remaining cases, the genetic cause is unknown.

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. A less common form of Huntington disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes. Additional signs of the juvenile form include slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired. Seizures occur in 30 percent to 50 percent of children with this condition. Juvenile Huntington disease tends to progress more quickly than the adult onset form; affected individuals usually live 10 to 15 years after signs and symptoms appear.

CAUSES:

Mutations in the HTT gene cause Huntington disease. The HTT gene provides instructions for making a protein called Huntington. 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 Huntington 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.

INHERITANCE PATTERN:

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. An affected person usually inherits the altered gene from one affected parent. In rare cases, an individual with Huntington disease does not have a parent with the disorder. As the altered HTT gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size. A larger number of repeats are usually associated with an earlier onset of signs and symptoms. This phenomenon is called anticipation. People with the adult-onset form of Huntington disease typically have 40 to 50 CAG repeats in the HTT gene, while people with the juvenile form of the disorder tend to have more than 60 CAG repeats. Individuals who have 27 to 35 CAG repeats in the HTT gene do not develop Huntington disease, but they are at risk of having children who will develop the disorder. As the gene is passed from parent to child, the size of the CAG trinucleotide repeat may lengthen into the range associated with Huntington disease (36 repeats or more).

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