Rotimi-Dairo Oluwatimilehin Victor

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**Developmental Genetics of Cerebellum**

**Introduction**

Cerebellum (Latin, ‘little brain’) major role is in role in sensory-motor processing that in the adult human contains more than half of all the brain's neurons. The adult cerebellum anatomy consists of three parts, the **vermis** (median) and the two **hemispheres** (lateral), which are continuous with each other.

The adult human cerebellum contains 69,030,000,000 ± 6,650,000,000 (sixty-nine billion thirty million) neurons and 16,040,000,000 ± 2,170,000 other cell types.

**Developmental Genetics of Cerebellum**

The cerebellum is derived from dorsal rhombomere 1, 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.

Disorder associated with cerebellar development

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 ofthis protein is normally increased in the bloodstream of pregnant women, but it isunknown 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 (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 ataxia telangiectasia varies greatly, but affected individuals typically live into early adulthood.

**Causes**

Mutations in the ATM gene cause 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 Qx 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 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 tumours.