**INTRODUCTION TO THE CEREBELLUM**

The Cerebellum is a part of the hindbrain which acts as a coordination cetre in humans, using sensory inputs from the periphery to fine-tune our movement and balance. Sensory information about movement and the position of the body-parts is sent to the so-called PRECEREBELLAR SYSTEM which is a group of nuclei in the brainstem. These nuclei with exception of the inferior olivary nucleus, in turn project to granule neurons, which communicate with the Purkinje cells of the cerebellum. The purkinje neurons provide the primary output from the cerebellar cortex projecting to the deep cerebellar nuclei. The neurons of the deep cerebellar nuclei finally project to the cerebral cortex, mediating the fine control of motor movements and balance.

Although the cerebellum is one of he first rain structures to differentiate, it achieves its mature configuration only many months after birth. This lengthy formative period makes the cerebellum especially vulnerable to developmental irregularities. In the past decades, genetic studies of mice have become the primary source of information about cerebellar development.

**GENES INVOLVED IN THE DEVELOPING PRIMORDIUM**

The neural tube can be thought of comprising of four regions during early development- the most anterior portion which is the prosencephalon which gives rise to the forebrain. The mesencephalon just caudal to the prosencephalon which gives rise to the midbrain, whereas hindbrain regions evolve from the metencephalon and myencephalon. Chick-Quail experiments have indicated that both the mesencephalon and metencephalon contribute to the developing cerebellum.

The proper patterning of the mesencephalon and metencephalon is dependent on molecular signals released from the Isthmus Organizer(IO). It has been shown in mouse mutanats, as well as in transplant experiments that the IO is necessary ans sufficient for patterning the mid/hindbrain region from the neural tube.

The IO is, in turn set up by the arrangement of a complex array of genes which are two in particular and are central to its development. One of which is the Otx2 (mouse homologue of the Drosphila gene) and the second is the the Gbx2 which is also a homologue of the Drosphia gene.

During embryonic development, Otx2 is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon whereas Gbx2 expression in the metencephalon is bounded anteriorly by caudal mesencephalon. The sharp boundary between between the expression domains of these two genes reflects the reciprocal repression.

In addition to helping form the IO molecularly, Gbx2 and Otx2 also regulate the expression of the fibroblast growth factor 8. Otx2 negatively regulates the fibroblast growth factor while Gbx2 maintains it. Mutant mice with a reduced level of the fibroblast growth factor 8(Fgf8) have a severe patterning defect of the mid/hindbrain region, which usually affects the cerebellum.

Fgf8 is a diffusable factor that exerts its action partially by inducing the expression of wingless homologue 1 (Wnt1) through Lim homeobox 1b ( Lmx1b). The wingless homolgue in turn, maintains te expression of Engrailed (En1) which then positively regulated Fgf8 expression completing this feedback regulatory loop. Mouse mutants of Wnt1, Lmx1b and En1 all show patterning defects of the mid/hindbrain.

Wnt1 and Lmx1b probably exert their influence through the action of En1. En2 which is a paralled homologue of En1 might also function in the patterning of the md/hindbrain. This En2 is expressed shortly after En1. Deletion of En2 against a haploinsufficient En1 bacground was accompanied by by a patterning defect in the mid/hindbrain region; similarly deletion of En1 against a haploinsufficient En2 mutant background also leads to an exaggerated phenotype.

There are other genes important in the patterning of the mid/hindbrain region- Pax2 and Pax5. These paired box genes are expressed in the mid-/hind-brain region. Pax2-null mice never develop a cerebellum or posterior mesencephalon although Pax5 mutants have only a mild phenotype in the mid-/hind-brain region. Pax2 and Pax5 might also be involved in the regulation of En1, Wnt1 and other patterning genes and together constitute another positive regulatory loop.

The Hox gene family which has an active role in patterning the hindbrain, seems to help restrict the development of the metencephalic structures into the myencephalon. For example, Homeobox 2(Hoxa2) which is the most anteriorly expressed Hox gene probably marks the caudal limit of the cerebellar anlage at the rhombomere 1. Mice without Hoxa2 develop enlarged cerebella. Less is known about the dorsoventral patterning in this region. Bone morphogenetic proteins and sonic hedgedog govern neuronal fates in the spinal cord and they have also been implicated in the dorsovental patterning of the mid-/hind-brain region. The bone morphogenetic proteins can induce the cerebellar granule neuron marker mouse atonal homologue(Math1) when expressed in the ventral region of the neural tube.

Hence, the reciprocal repression of Otx2 and Gbx2 forms the IO which in turn uses Fgf8 and En1 to pattern the prospective mid-/hind-brain region. Cells from both the mesencephalon and the metencephalon give rise to cerebellar tissues.

**GENES INVOLVED IN THE DEVELOPMENT OF PURKINJE AND GRANULE CELLS**

The purkinje, golgi and stellate cells all arise from the ventricular epithelium. Relatively little is known about the specific factors that govern Purkinje Cell differentiation. Shortly after the final mitosis of Purkinje cells they begin to express the calcium-binding protein calbidin. Calbidin positive cells migrate in a radial direction over the already formed deep cerebellar nuclei. The timely arrest of migration is dependent on the reelin pathway. Purkinje cells develop extensive dendritic arbors and synapse onto granule neurons in their final maturation phase and it depends on thr granule neuron signals. Because of the role of the Wnt3 gene in axon and dendrite development,it is a good candidate for influencing this phase of development. Throughout the course of development, various growth factors are important for Purkinje Cell survival- Nerve growth factor, acetycholine, neurotropin 4/5, brain derived neutrophic factor and ciliary neutrophic factor. All factors listed above all show a postive effect on Purkinje cell number in vitro.

Unlike all other cerebellar cells which are derived from the ventricular zone, the granule neurons derive from a separate germinal epithelium known as the rhombic lip. Tis rhombic lip is located between the fourth ventricle and the roof late in the metencephalon. Expression of the Math1 gene governs the germinal epithelium of the rhombic lip. A mice which is null of Math1 lacks several rhombic lip derivatives including the granule neurons of the cerebellum and the pontine nucleus of the precerebellar system.

Chick-quail chimaera experiments have shown that the rhombere 1 region of the rhombic lip is the probable source of the granule neuron receptors. This is futher supported by the analysis of Hoxa2 mutanats, which have an expanded rhombomere 1 and increased number of granule neurons. Fairy on in development, rhombic lip cells are specified to become granule neurons although the roles of the transcription factors( Math1,RU49/Zipro1, Zicl and Zic3) are during the migration of rhombic lip cells.

Rhombic lip cells continue to migrate to the cerebellar anlage and settle on its periphery to become the EGL(External Granular Layer). Granule neuron precursors in the outer EGL express several markers including Math1, RU49/Zipro1 and Zic1. The over expression of RU49/Zipro1 leads to an increase in the number of granule neurons and increase in proliferation in the outer EGL.

The Purkinje cells are particularly important in the control of cell proliferation of the precursors in the outer EGL. Defects in the purkinje cells lead to a decreased number of granule neurons. Genes involved in the cell cycle are also important in cerebellar granule proliferation. Cyclic D2 is a brain-specific cyclin found in the cerebellum and animals that lack it have fewer granule neurons and stellate interneurons.

From the outer EGL, granule neuron precursors migrate into the inner EGL. Cells in the inner EGL are postmitotic and are in a state of premigration. The change from the proliferating to postmitotic states might involve the accumulation of cell-cycle inhibitors.

The final stage of the maturation of granule neurons occurs in the IGL. At this point, granule neurons are expressing mature markers such as GC5 and GABA receptors and mossy fibers get in contact with the granule neurons. This develpomental process is partly controlled by Wnt7a, which is released by granule neurons.

(2001, vol. 2 macmillian magazines ltd)

2a) FRIEDREICH ATAXIA- It is an inherited condition that affects the nervous system and causes movement problems. People with this condition develop impaired muscle coordination(ataxia) which worsens over time.

Genetic basis of Friedreich Ataxia- It is caused by mutations in the FXN gene. This gene provides instructions for making a protein called frataxin. One region of the FXN gene contains a segment of DNA known as GAA trinucleotide repeat. This segment is made up of a series of three DNA building blocks (one guanine and two adenines) that appear multiple times in a row. Normally, this segment is repeated 5 to 33 times within the FXN gene but people with this ataxia have the GAA segment repeated 66 to more than 1,000 times. This abnormally long GAA trinucleotide disrupts the production of frataxin which severely reduces the amount of protein in cells and certain nerve and muscle cells cannot functio properly with a shortage of frataxin hence, the signs of ataxia.

b) OLIVOPONTOCEREBELLAR ATROPHY- This condition is characterised by degeneration of nerve cells in certain areas of the brain. Genetic forms of OPCA may be inherited. For example the OPCA associated with spinocerebellar ataxia 3 is caused by an extended stretch of the CAG triplets in the coding region of the ATXN3 gene on chromosome 14q32.1. This gene helps in proteasomal protein degradation pathway.