DEVELOPMENTAL GENETICS OF THE CEREBELLUM

ONYEMA FAVOUR CHINAZAM

17/MHS01/266

ABSTRACT

The mammalian central nervous system is one of the most complex biological systems to understand at the molecular level. The development of cerebellum based on genetics is due to the expression of the sonic hedgehog which is an important gene in the body. There are many other genes also responsible for the development of the cerebellum and all these are discussed in the review. Abnormalities associated with developmental disorders of the cerebellum are also discussed in this concise review.

INTRODUCTION

The cerebellum is a part of the central nervous system which is located posterio-inferior at the base of the brain. The cerebrum is located above it and the pons in front of it. The cerebellum resides at the anterior end of the hindbrain and is classically defined by its role in sensory-motor processing. It is a part of the brain that functions in motor control. It originated from the Latin word which means small brain.

Organs are formed by interactions between cells and tissues. This is due to induction of cells caused by another set of cells that results in differentiation of the cells according to their functions. This induction process occurs in cerebellum and involves epithelial to mesenchymal interactions through cell to cell signaling that is established by paracrine interactions. Paracrine interactions include a lot of factors which are categorized into four main groups or families. The sonic Hedgehog is the most expressed gene in the cerebellum among these four groups and it is a morphogenetic factor that is involved majorly in cerebellar patterning and foliation. It controls the proliferation of progenitors in the cerebellum.

DISCUSSION

All cerebellar neurons are produced in the alar plate of r1 that is located rostrally adjacent to the isthmus. In this region, the dorsalmost part of the neuroepithelium gives rise to the roof plate while the ventrally and intermediately located parts become the ventricular zone (VZ) and the rhombic lip (RL). As stated before many genes assist in the development of the cerebellum. The Sonic Hedgehog Gene (Master Gene for Development), two basic-helix-loop-helix (bHLH) proteins, Atonal homolog 1 (ATHO1 also called MATH1) and Pancreatic transcription factor (PTF1a) [participate in the specification of the spatial identities of cerebellar progenitors], Engrailed-2 Gene (En1/2), Achaete-scute homolog 1 (Asc1), Retinoic-Acid-Related Orphan Receptor Alpha Gene (Rora), Reelin (RELN) and Chemokine Receptor 4 (CXCR4)& Chemokine Ligand 12(CXCL12) System.

Engrailed-2 Gene is a homeobox factor familywhich is important for the patterning of cerebellar lobules and purkinje cells protein stripes. En1/2 are expressed in spatially restricted patterns in most cell types during early post-natal development of the cerebellum and are implicated in neurodevelopmental disorders. It regulates the targeting of the mossy fiber system to subsets of cerebellar lobules and En1/2 mRNA/protein are expressed in the ventricular zone.

Rora is a transcription factor for encoding a retinoid-like nuclear receptor which is highly expressed in the cerebellum. It belongs to the steroid-thyroid hormone receptor superfamily. It acts as a constitutively active nuclear receptor and is expressed in the glial cells especially in the astrocytes.

Atonal homolog 1 (ATHO1 also called MATH1) is a transcription factor of the bHLH class and functions in the specifications and differentiation of the glutamatergic lineages. MATH1 is important for proper development of the granular layer of the cerebellum and it develops interneurons that give rise to spinocerebellar and cuneocerebellar tracts.

Pancreatic transcription factor (PTF1a) is a factor responsible for development of purkinje cells and GABAergic interneuron and is derived from PTF1a domain. PTF1a is involved in the control of fate and survival of neurons during development.

Achaete-scute homolog 1 (Asc1) directs ventricular neuroepithelium progenitors toward inhibitory interneuron fate and suppresses the astrocystic differentiation and also maintains balance between oligodendrocytes and astrocytes.

Reelin (RELN) is an extracellular matrix component attracting or repealing precursors and axons during development. It is secreted by the external granular layer which promotes Purkinje cell migration. RELN acts as an extracellular signaling molecule. It exerts its influence after birth and modulated long term potentiation which is involved in learning. In adult brain, RELN regulates structural and structural properties of synapses and controls the developmental processes remaining active.

Chemokine Receptor 4 (CXCR4) & Chemokine Ligand 12(CXCL12) System are important in cell migration and in organogenesis. CXCR4 attract the cerebellar granular neuronal precursors to the outer external granular layer and promote an increase of the sonic hedgehog mitogenic effect.

The Sonic Hedgehog Gene (Master Gene for Development) is highly expressed in the cerebellum and involves the GLI family of the transcription factors. It is the most important gene in the cerebellar development. Hedgehog binding to transmembrane receptor Patched 1 triggers a cascade of events tuning cAMP production. Cholesterol is an activator of Sonic Hedgehog which stimulates very strongly the proliferation of cerebellar granular neuronal precursors through the induction and the repression of cell cycle regulators genes. It also promotes Bergmann glia proliferation and thus contributing to the migration support.

CEREBELLAR DISORDERS

Cerebellar disorders affect the maintenance of balance and equilibrium function of the cerebellum. They are not very common and the focus in this review would be on the genetic bases of cerebellar disorders. Such disorders are:

- Friedreich ataxia is an inherited cerebellar disorder that affects the nervous system and causes movement problems. It is caused by the mutation of FXN gene which provides instructions for making the protein Frataxin. In

this condition the segment of GAA is repeated 66 to 1000 times within the FXN gene. This causes difficulty in walking, impaired muscle coordination, muscle stiffness, impaired speech and loss of strength and sensation in the arms and legs. Treatment includes physical and occupational therapy.

- Autism Spectrum Disorder is a term used to describe a group of neurodevelopmental disorders. It has many etiologies but it can be caused by genetic mutation of the En1/2 gene and the Reelin gene. There is no cure for autism but therapies such as behavioral, play, occupational, physical and speech therapy can be used as treatment.

- Cerebellar Agenesis is a rare condition in which a brain develops without the cerebellum. It is caused by the mutations in the PTFA1 gene. Symptoms include severe developmental delays, language deficit and neurological abnormalities. It is fatal on its own but can co-exist with other malformations like anencephaly, holoprosencephaly and microencephaly.

- Lissencephaly is a set of rare brain disorders where the whole or parts of the brain appear smooth and devoid of convolutions. Some forms are caused by the mutation of the Reelin gene. Symptoms here include severe psychomotor impairment, failure to thrive, seizures and muscle spasticity.

- Hypoplasia of the cerebellum is also a disorder of the cerebellum in which the cerebellum is smaller than usual or not completely developed. It is a feature of a number of congenital malformation syndromes. It might also be due to a problem or mutation of the sonic hedgehog gene. There is no standard treatment of this condition and most treatments are symptomatic and supportive.

CONCLUSION

The Sonic Hedgehog Gene (Master Gene for Development), Atonal homolog 1 (ATHO1 also called MATH1) and Pancreatic transcription factor (PTF1a), Engrailed-

2 Gene (En1/2), Achaete-scute homolog 1 (Asc1), Retinoic-Acid-Related Orphan Receptor Alpha Gene (Rora), Reelin (RELN) and Chemokine Receptor 4 (CXCR4)& Chemokine Ligand 12(CXCL12) System are all the factors and genes responsible for the development of the cerebellum. Mutation or damage to this gene causes disorders to the cerebellum and affects coordination, equilibrium, speech, eye movement etc.

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