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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.

CEREBELLAR DEVELOPMENT AND THE BASES OF CEREBELLAR DISORDERS

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ABSTRACT

The cerebellum known as the little brain was discovered by Vesalius but was described more carefully by Thomas Willis in 1664. Since then, more of its anatomic features were identified and its role in coordinating movement was acknowledged. The Cerebellum is particularly involved in the spectrum of neurodevelopmental diseases; to be more precise, ataxias. In recent years, the comprehension of some of the more familiar aspects of cerebellar development, such as its territorial allocation and the precursor site of several of its cells types, has undergone significant changes. In addition, due to its stereotyped circuitry across different species, insights from a variety of species have contributed to an increasingly accurate picture of how this system develops and what disease may evolve because of molecular damage to its cells. This review intends to discuss the underlying causes of congenital disorders and examine the genetics behind such disorders.

Keywords: Cerebellum, neurons, GaBAergic, Glutamergic, fate mapping, Ataxia, vermis, ventricular zone, rhombic lip.

INTRODUCTION

Before the introduction of genetic fate mapping, most of the research on the cerebellum has been based on its circulatory. However, recent findings have brought to light the development of its intricate structures and further studies have shown that embryonic disarray of such structures are the leading causes of the most common developmental cerebellar disorders.

Various genes have been noted specifically for the causes of cerebellar developmental disorders. Hereto, these genes have been classified and have lead to a new molecular basis for common cerebellar diseases. Most of these researches and studies that have been carried out on mice and appears to a high level of agreeability, attest to that in man.

THE DEVELOPMENT OF THE CEREBELLUM

To discuss the subject of cerebellar disorders, it is imperative to highlight the origin and development of the cerebellum.

The cerebellum is located in the anterior boarder of the hindbrain. Along with the pons, the cerebellum has its embryonic origin from the metencephalon.

The cerebellum develops from the rhombic lip which is the dorsolateral part of the alar plate of the metencephalon, it forms the rostral boarder of the 4^{th} ventricle. Two rounded swellings develop due to migration of cells from the alar plate- This swellings constitute the primordial hemispheres of the cerebellum. As development continues, the primordia expand medially towards the roof plate of the metencephalon and eventually fuse. At this stage, the two lateral spheres of the ventricle are visible and the vermis can be identified in the middle.

The primordial cerebellum lies along the anterior/posterior axis of the neural tube. According to Millen and Gleeson (2008) the positioning of the primordial cerebellum is under the influence of signaling from both the isthmic organizer and fourth ventricle roof plate. The isthmic organizer sends out the Fgf and Wnt signals while the roof of the fourth ventricle secretes Bmp (bone morphogenic proteins), Wnt and retinoic acid. Using fate mapping experiments pertaining to mouse, it has been noted that in early embryogenesis, the rhombomere rotates by 90 degrees, changing its rostral-caudal axis to a medial-lateral axis of the wing-like bilateral cerebellar primordial.

The mature cerebellum accounts for more than 50% of the neuronal bodies in the brain. During development, the neurons of the cerebellum arise from two origins

- The ventricular zone
- The rhombic lip

Early in the cerebellar development, cells derived from the rhombic lip migrate to form a layer over the surface of the cerebellar primordial. This layer constitutes the external germinative layer (EGL) and later on the remaining cells of this layer migrate radially into the cerebellum. The ventricular zone expands to give rise to neuroblasts that develop into the radial glia, cerebellar nulei and purkinje cell (efferent neurons of the cerebellar cortex). Extroversion of the primordial cerebellum occurs when the EGL starts to migrate in an outward inward fashion through the purkinje cell layer beneath . The speed of migration within the EGL is driven by diffusible sonic hedgehog (Shh) secreted by underlying Purkinje cells (Dahmane and Ruiz-i-Altaba, 1999; Wallace, 1999; Wechsler-Reya and Scott, 1999; Lewis et al., 2004). As these cells of the EGL transverse through the purkinje cell layer, they convert it from a mutilayered organization into a single layer.

According to Millen and Gleeson (2008), the two regions of the cerebellar cell origin have specific transcription factors; the bHLH factor Ptf1a (pancreas transcription factor 1 alpha) is expressed in the ventricular zone and the bHLH factor Math 1 (protein atonal homolog 1) is expressed in the rhombic lip zone. Scientific experiments and fate mapping have led to proving that Ptf1a and Math1a are not merely transcription markers for cerebellar progenitor zones but also aid cerebellar neuronal specifications.

According to Hoshino (2005), Ptf1a is responsible for the correct generation of GaBAergic neurons and subtypes in the ventricular zone. The main GaBAergic neurons of the cerebellum include; purkinje cells, stellate and basket cells, and in the absence of Ptf1a, these cells fail to develop. Fate mapping experiments of mice shows that the ventricular zone produces neuronal precursor cells, but for these cells to specify into GaBAergic neurons, Ptf1a is required. It was noted that the loss of Ptf1a in mice caused failure in production of cerebellar GaBAergic neurons. In another experiment in mutated wild mice which lacked Ptf1a, the precursor cells produced by the ventricular zone migrated to the rhombic lip zone and exhibited markers such as Math1, reelin and Zic1/2 which were found in in rhombic lip cells. This implies that the fate of the progenitor cells is dependent on

the transcription factors, and a change in such factor can result in the production of an entire different cell. As stated by (Millen et al., 2014) , loss of Ptf1a also leads to mixing between dorsal and ventral (non-cerebellar) ventricular derivatives. These results suggest a dynamic segregation of lineages that is dependent on their genetically determined post-mitotic identity.

Scientific research has proven that the rhombic lip which expresses Math1, is the region where precursor granular cells are derived from. Further research using fate mapping on mice shows that the math 1 transcription factor is not only neede for producing granular cells but is also involved for creating all know glutamatergic neurons of the cerebellum. Although, Math1 factor is involved in making glutanergic neurons, there is no evidence to verify that it transforms the fate of the precursor neuronal cells.

Since neuronal precursor cells lineage is dependent on the transcriptional factor, how can the expression of these genes in precursor cells noted?. Research has determined that both RL induction and Math1 expression is dependent on Bmp-derived signals from the adjacent roof plate. Further, the roof plate Bmp signal is countered by antagonistic Notch1 activity within the cerebellar ventricular zone. “Thus, antagonism between the Notch and BMP signaling pathways regulates the differentiation of cerebellar progenitors throughout the period of cerebellar neurogenesis” (Millen and Gleeson 2008).

CEREBELLAR DISEASES

Cerebellar Ataxia

Cerebellar Ataxias are a group of disease which results from damage to the cerebellum. Ataxias are characterized by loss of motor coordination, hypotonia(loss of muscle tone), impaired mental development. These diseases can be caused by a number of factors, but until recently, genes which caused congenital cerebellar ataxia have been identified.

The Ptf1a (pancreas transcription factor 1 alpha) a gene which caused neonatal diabetes was identified in patients with congenital cerebellar ataxia. As stated earlier, this gene is required for the formation of GaBAergic neurons in the cerebellum. Deletion of the Ptf1a gene not only causes absence of GaBAergic neurons but also leads to death of glutamergic neurons at birth. The glutamergic neurons die out because of absence of GaBAergic neurons to synapse with. This

has increased the understanding of cerebellar development and the causative genes for ataxia.

Joubert Syndrome

Joubert syndrome is a congenital cereballar ataxia. It is easily identified by its characteristic cerebellar and brain stem malformation called the molar tooth. Symptoms of the Joubert syndrome are present from neonatal period. These signs include hypotonia which progresses to ataxia, ocular motor apraxia, breathing dysregulations. The symptoms of Joubert syndrome are usually related with multiple organs mainly the retina, kidney skeleton and liver.

Genetics of the Joubert syndrome

According to research, the causative genes of the Joubert syndrome are all related to the primary cilium (an immotile organelle that protrudes from the surface of nearly all cell types). Dysfunction of this organelle leads to this syndrome (Romani, Micalizzi and Valentente, 2013).

CONCLUSION

The cerebellum is an important part of the brain which functions to coordinate muscle movement, maintain posture and balance. The recent studies in mice has enabled us to understand the cells of the cerebellum and its development. This has led to a breakthrough in determining the causes of several neonatal and adult life defects of the cerebellum such as the aforementioned ataxia.

In addressing this subject matter, it has been made clear that various genes account for many congenital cerebellar defects. The gene Ptf1a has been identified as a major player in the proper development of the cerebellar cells. Hence, understanding the cerebellum does not only require a surface level research on its function and circulatory unit but a deep knowledge of its intricate structures as they are the real causes of congenital cerebellar diseases.

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