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QUESTIONS

1) Write a concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorders

ANSWERS

THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM

The cerebellum is one of the first brain structures to begin to differentiate, yet it is one of the last to achieve maturity and its cellular organisation continues to change for many months after birth. Over the past few years, genetic research has provided a great deal of information about the molecular events directing the formation of the cerebellum.

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 fine-tune our movement and balance.

NOTE: The study of mouse homologues of DROSOPHILA GENES has provided valuable insights into the molecular basis of cerebellar development.

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 specialised germinal matrix called the RHOMBIC LIP.

Cerebellar neurogenesis is compartmentalised in relationship with neurotransmitter fate.

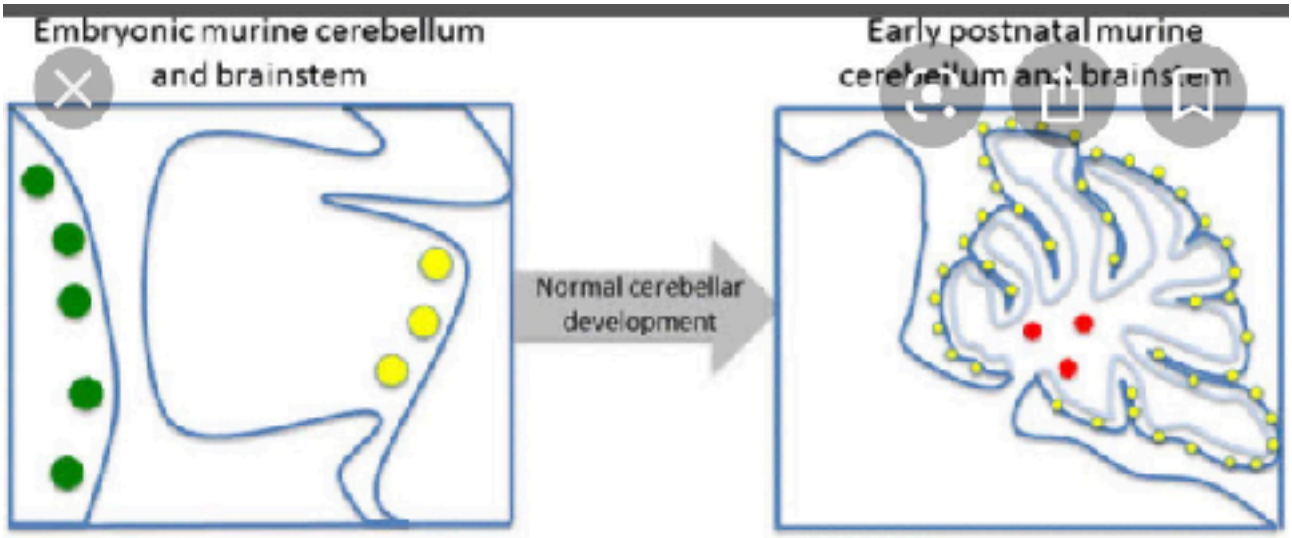
The ***Engrailed-2-gene*** is a major actor of the specialisation of cerebellar cell types and late embryonic morphogenesis. The engrailed(En) homebox transcription factor family is critical for the patterning of cerebellar lobules and for purkinje cells protein stripes. The En1/2 regulates the targeting of mossy fibre systems to subsets of cerebellar lobules, showing a main role for the afferent topography in the cerebellar circuitry.

Math 1, expressed by the rhombic lip, is required for the genesis of glutamatergic neurons. It is critical for the proper development of the granular layer of the cerebellum.

Mutants deficient for the transcription factor ***Ptf1a(pancreatic transcription factor 1a)*** display a lack of purkinje cells and gabaergic interneurons. It is also involved in the control of fate and survivel of nearons during development.

Rora gene(Retinoic Acid Related Orphan Receptor Alpha Gene) contributes to the developmental signalling between granule cells and purkinje neurons. Rora is a transcription factor encodeing a retinoid-like unclear receptor which is highly expressed in the cerebellum. It also protects neutrons against oxidative stress and shows an anti inflammatory action by inhibiting the NF-Kappa-B pathway

The expression profile of ***sonic hedgehog*** in postnatal stages determines the final size/shape of the cerebellum. Sonic hedgehog is a morehogenetic factor which is a masterly in a cerebellar patterning and foliation. Genes affecting the development impact upon the physiological properties of the cerebellar circuits. For instance, receptors are developmentally regulated and their action interferes directly with developmental processes. Another field of research which is expanding relates to very preterm neonates. They are at risk at cerebellar lesions,



Cell of origin	Dorsal brainstem precursor	Granule cell precursor	Cerebellar stem cell
Genetics	Monosomy 6, CTNNB1 mutation	PTCH, SMO and SUFU mutations, Gli2 and MYCN amplification	i17q, MYC amplification
Gene expression	WNT signaling	SHH signaling	MYC+++
Predominant Histology	Classic	Desmoplastic/nodular	Large cell/anaplastic
Prognosis	Very good	Intermediate	Poor

which may themselves impair the developmental events. Very preterm neonates often show sensori-motor deficits, highlighting another major link between impaired developments and learning deficiencies. Pathways playing a critical in cerebellar development are likely to become therapeutical targets for several neurodevelopment disorders.

SOME GENETIC BASES OF CEREBELLAR DISORDERS

There is currently a growing awareness that neurodevelopment disorders are associated with cerebellar deficits and learning impairments. Still, the molecular mechanisms of the cerebellar defects remain poorly understood in many cases.

A) JOUBERT SYNDROME:

The disorder presents with developmental delay, hypotonia, impaired respiration, abnormal eye movements and ataxia. Motor learning is strongly impaired. The 'Molar Tooth Sign' (deep interpeduncular fossa, enlarged superior cerebellar pedants which are more horizontally oriented and hypoblastic cerebellar vermis) is very suggestive. It is associated with mutations of genes encoding components of the primary cilia. Interestingly, primary cilia are determined for sonic hedgehog signal transduction.

Disruption of primary cilia formation blocks the proliferation of neural progenitors of granule cells mediated by sonic hedgehog.

B) RHOMBENCEPHALOSYNAPSIS:

It is associated with learning disabilities. It is a malformation of the hindering characterised by fusion of the cerebellar hemispheres and dentate nuclei. An association with mutations in the MN1 gene(meningioma (disrupted in balanced translocation)) 1 has been reported in cases of atypical rhomboencephalosynapsis.

C) DANDY-WALKER MALFORMATION

Sonic hedgehog might also be involved in the pathogenesis of Dandy-Walker malformation through a contribution of Zinc finger transcription factors which modulate the sonic hedgehog pathway

D) AUTISM:

They are characterised by difficulties in communication, social skills and repetitive behaviour. Cerebellar networks might be critically involved in the pathogenesis of autism. The expression of IL-6 is increased in the cerebellum of autistic patients. IL-6 impacts upon the development

of the cerebellum, impairing neural cell adhesion, migration and causing an excessive formation of excitatory synapses.

E) SMITH-LEMLI-OPITZ SYNDROME:

It is an autosomal recessive syndrome with multiple congenital malformations , which is due to defects of cholesterol homeostasis. Hypoplasia is associated with this syndrome. Blocking GLI2 causes a failure in the development of cerebellar granular near onal precursors, ending in cerebellar hypoplasia.

REFERENCES

- PASQUER et al., 2009
- ARGUA, 2004
- WEI et al., 2011