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NEUROANATOMY ASSIGNMENT

# QUESTION

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

NB: As usual observe every research or scholarly writing rule.

Organs are formed by interactions between cells and tissues. Most often, one group of cells or tissues cause another group of cells or tissue to change their fate, a process known as INDUCTION.

The induction process of the cerebellum involves epithelial to mesenchymal interactions. These epithelial cells are joined together in sheets, whereas mesenchymal cells are fibroblastic in appearance and dispersed in extracellular matrices.

Cell to cell signaling is essential for induction, for crosstalk between inducing and responding cells, hence these lines of communication are established by paracrine interactions, whereby proteins synthesized by one cell diffuse over a short distance to interact with other cells.

There is a large number of paracrine signaling factors acting as ligands which are also called GDFs. Most are grouped into four families, and members of these same families are used repeatedly to regulate the development and differentiation of organ systems.

Of the four families, the sonic hedgehog is highly expressed in the cerebellum. The sonic hedgehog is a morphogenetic factor which is a master player in cerebellar patterning and foliation. It also controls the proliferation of progenitors in the cerebellum. For example, sonic hedgehog stimulates very strongly, the proliferation of cerebellar granular neuronal precursors through the induction and repression of cell cycle regulator genes. In addition, sonic hedgehog contributes to the development of cerebellar cortex development by promoting Bergmann glia proliferation.

Sonic hedgehog pathway, involves the GLI family of transcription factors. The binding of sonic hedgehog to trans membrane receptor Patched 1 triggers a cascade of events tuning cAMP production. (cholesterol is the activator of sonic hedgehog)

The extracellular matrix undergoes a substantial remodeling during cerebellar development providing cues for division or differentiation according to its content. Laminin and heparin sulfate proteoglycans increase the mitogenic effects of sonic hedgehog.

Sonic hedgehog pathway is also controlled by negative regulators, such as PACAP (Pituitary adenylate-cyclase activating polypeptide). Sonic hedgehog is also deactivated by FGF-2, which triggers the differentiation of neural precursors of granule cells.

GENES INVOLVED IN CEREBELLAR DEVELOPMENT ARE;

1) The Engrailed-2 Gene (En 2 Gene).

The engrailed (En) homeobox transcription factor family is critical for the patterning of cerebellar lobules and for Purkinje cells protein stripes.

2) Math1.

The specification and differentiation of glutamatergic lineages is dependent upon Math1, a critical transcription factor of the bHLH class. It is critical for the proper development of the granular layer of the cerebellum.

3) Ptf1a and Ascl1.

Pancreatic Transcription factor 1a (Ptf1a);

- Helps in the development of Purkinje cells and gabaergic interneurons.
- Climbing fiber neurons are derived from the Ptf1a domain.

These climbing fiber neurons then mature, migrate and differentiate causing the formation of olivary nucleus.

- Ptf1a is also involved in the control of fate and survival of neurons during development.

Ascl1;

Directs ventricular neuroepithelium progenitors toward inhibitory neuron fate and suppress astrocytic differentiation.

#### 4) Rora (Retinoic- Acid- Related Orphan Receptor Alpha) Gene.

Rora belongs to the steroid-thyroid hormone receptor superfamily. Its endogenous ligand is cholesterol which is abundantly present in each cell.

Rora is a transcription factor encoding a retinoid like nuclear receptor which is highly expressed in the cerebellum, plays a pivotal role in its development. Rora functions extend beyond development, it also protects neurons against oxidative stress and shows an anti-inflammatory action by inhibiting the NF- kappa- beta pathway.

#### KNOWN CEREBELLAR DISORDERS.

Deficiency in the genes responsible for the development of the cerebellum or interruption in the sonic hedgehog signaling pathways lead to cerebellar disorders. These disorders are disorders of equilibrium and they are;

- 1) Ataxia – Inability to maintain the equilibrium of the body, while standing or walking.
- 2) Asynergia – Lack of coordination of muscles which also interferes with purposeful movement. Movements are jerky and lack precision.
- 3) Dysarthria – Incoordination of the muscles responsible for the articulation of words leading to characteristic speech defects.
- 4) Nystagmus – Incoordination of the muscles of the eye, the eyes are therefore unable to fix the gaze on an object for any length of time.