SESSION 1T

BRAIN FUNCTION, DYSFUNCTION AND REPAIR

Session Moderator: Kathleen Millen, Pediatrics

JHN 175

12:30 PM to 2:15 PM

* Note: Titles in order of presentation.

Premature Migration of Cerebellar Granule Cells due to Disrupted Fetal Mesenchymal Signaling Drives Heterotopia Formation in Dandy Walker Malformation

Danilo Dubocanin, Senior, Biochemistry
UW Honors Program
Mentor: Kathleen Millen, Pediatrics, Seattle Children's Research Institute

Heterotopia are organized structures consisting of mixed cellular and neuronal elements arranged in a clear architectural pattern inappropriate to the considered tissue. Heterotopia are observed in the cerebral cortex and the cerebellum as a feature of many neurological disorders yet the we know little about the mechanisms driving their formation. We have analyzed a substantial number of Dandy Walker malformation (DWM) human fetal cerebella and found that a significant number of cases contain heterotopia. DWM is the most common structural birth defect of the human cerebellum and is characterized by an enlarged posterior fossa, enlarged fourth ventricle, and cerebellar vermis hypoplasia. A subset of cases are caused by loss of FOXC1, a transcription factor expressed in the mesenchyme during development. Our group has previously shown that loss of FOXC1 in mice causes loss of the mesenchyme-secreted factor SDF1alpha. Further, loss of SDF1alpha is sufficient to cause cerebellar heterotopia. This emphasizes the importance of mesenchymal signaling in the maintenance and development of the clear laminar architecture of the mature cerebellum. We hypothesized that granule neuronal progenitors (GCPs) are the primary cellular target of SDF1alpha mesenchymal signaling and therefore the main cell type causing heterotopia formation. To test our hypothesis, we excised the receptor for SDF1alpha from just GCPs in mice. Our findings show that loss of SDF1alpha in GCPs causes them to prematurely migrate into the developing cerebellar anlage and also caused other cerebellar cell types to form structured heterotopia. We observed defects in cerebellar foliation in the treatment group. Our data emphasizes the importance of SDF1-alpha dependent mesenchymal signaling in cerebellar development and identifies heterotopia as a new phenotype in DWM.

POSTER SESSION 2

MGH 258, Easel 182

1:00 PM to 2:30 PM

Defining the Pathology of Human Dandy Walker Malformation

Tarika Sivakumar, Senior, Biochemistry
Mentor: Parthiv Haldipur, Pediatrics, Seattle Children's Research Institute
Mentor: Kathleen Millen, Pediatrics, Seattle Children's Research Institute

Dandy Walker malformation (DWM) is the most common human cerebellar malformation, affecting 1 in every 3000 live births. DWM is an imaging diagnosis that is characterized by three features: cerebellar vermis hypoplasia, an enlarged posterior fossa, and an enlarged fourth ventricle. Although recent advances in neuroimaging have improved diagnosis of DWM, virtually nothing is known about the cellular and histological defects that lead to DWM. One major reason is that little human specific data is available describing the histology of normal and abnormal human fetal cerebellar development. Currently, there is limited published fetal pathology of DWM. There is no comparative analysis available and most studies are confounded by lack of molecular confirmations of diagnoses. We have carried out the first comprehensive histo-pathological analysis of human DWM. Such histopathological analysis, that I specifically was responsible for completing, included measuring the length and cell density of certain regions of the developing cerebellum in the 36 DWM cases, such as the external granule layer and the rhombic lip. Our results indicate a significant reduction in size and area of neuronal progenitor zones in the developing human cerebellum. We also observe aberrations in the developmental trajectories of specific cell types like Purkinje cells, and progenitor zones like the rhombic lip. Through our analysis of the human fetal DW cerebellum, we begin to directly address the developmental pathology of human DWM beyond that of the mouse models that share similar pathology. We believe our studies will fundamentally improve our view and understanding of the biology of the human cerebellar development and

give us insights on the developmental pathogenesis of DWM.