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praveen mohanraju

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Mohanraju P1, Clark KCl, George NM1,2, Benusa SD1,2, Dupree JL1,3

Department of Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine1; Hunter Holmes McGuire VA Medical Center2

Multiple Sclerosis

Incidence: 2.3 million people worldwide diagnosed with MS

Immune-mediated disorder of the CNS where healthy myelin tissues are damaged

Symptoms:
- Cognitive dysfunction
- Visual disturbances

Background

The axon initial segment (AIS) is fundamental for neuronal communication and action potential modulation, a characteristic which has been shown to be disrupted in inflammatory diseases such as Multiple Sclerosis. Previous work has portrayed evidence of AIS breakdown in layer 5 of the cortex, which was independent of demyelination in experimental autoimmune encephalomyelitis (EAE) induced mice. It has also been found that AnkyrinG, is an essential cytoskeletal scaffolding protein necessary for proper AIS function. It further promotes clustering of necessary AIS proteins and voltage-gated sodium channels. AnkyrinG deficiency results in a non-functional AIS. Therefore, AIS stability is critical for neuronal function. Furthermore, in order to determine if the pathology is specific to the cortex or affects other regions of the brain in the EAE model, we investigated the hippocampus, a region associated with cognitive dysfunction in several inflammatory diseases.

AIS Stability in MS

Figure 1. MS brains (B) display significantly fewer AISs (C) than aged-matched non-MS brains (A). (ankyrinG, red) p<0.05

The EAE Model

Figure 2. Mice are induced for EAE with an injection of MOG+CFA accompanied by pertussis toxin. *8 days post injection (dpi), mice show initial signs of disease; *14 dpi mice reach peak disease based on clinical symptoms, and analyses are conducted 3 (Early) and 9 (Late) days post peak.

AIS Stability in EAE Hippocampus

Figure 4. AISs are observed in the dentate gyrus (A,B) and CA1 (C,D) of the hippocampus. No overt differences were observed in the number of AISs in these region between Naive and EAE mice. Quantitative analysis was in vain due to extensive overlapping and clustering of the AISs (ankyrinG, red). Western blots of hippocampal homogenates from Naive, Late EAE, and Chronic EAE reveal no breakdown of Beta IV Spectrin (E).

Conclusion

- Immunohistochemical (IHC) labeling for ankyrinG combined with laser confocal microscopy display an inefficient method of quantifying AISs in the hippocampus
- Preliminary data illustrates no breakdown of AISs in the hippocampus as observed in the cortex
  - Western blots display Beta IV Spectrin breakdown in the cortex, but not in the hippocampus

Future Directions

- Microglial morphology in the cortex and hippocampus will be assessed to determine if a difference in activation results in AIS breakdown or preservation
- Microglia are enigmatic and are known to play different roles in different regions of the brain. Therefore, we are interested in isolating these cells from the hippocampus and from the cortex to compare microglial expression profiles
- Findings from these studies should shed light on the role microglia play in different brain regions during disease.

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