Impact of enterobacterial infections on the nervous system

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Background

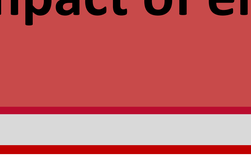
- Enterobacterial infections cause damage to the enteric nervous system and can result in cognitive impairment.
- Altered gut microbiome compositions detected in Alzheimer's disease (AD) and other neurodegenerative disease patients.
- Microtubule associated protein tau (Mapt, or tau), is abnormally phosphorylated in the AD brain
- Tau is present in neurons in both the CNS and the ENS but has not been implicated in enterobacterial-induced neurodegeneration.

Goal: to evaluate the role of neuronal tau in the gut neuroimmune responses to the enterobacterium *Shigella sonnei.*

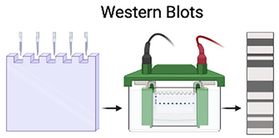
Hypothesis: Neuronal tau is expressed by the ENS and in response to infection, shifts in tau phosphorylation occur in the gut, resulting in neuronal loss.

Methods

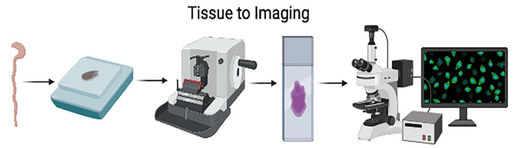
B6 and Mapt -/- mice infected with the bacterium *S. sonnei*



Behavioral tests to measure cognitive abilities

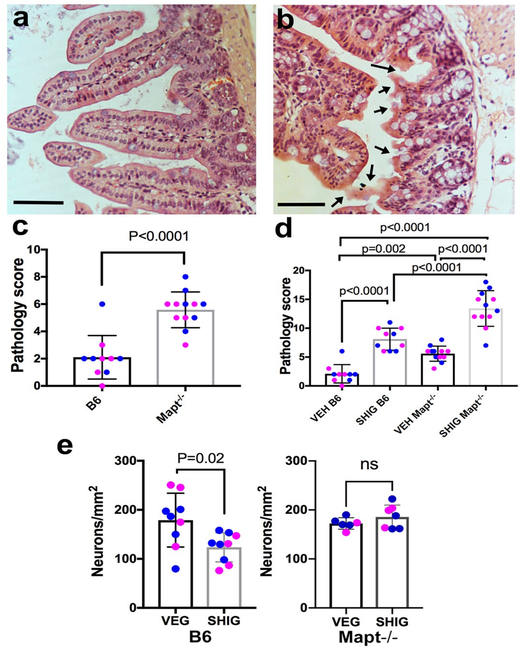


Analyzing tissue for presence of tau and phosphorylated tau proteins

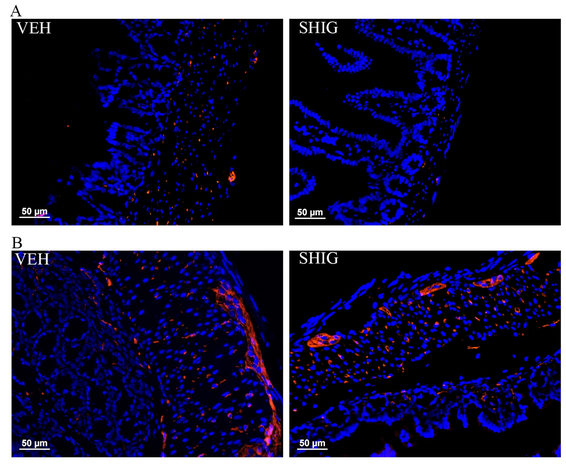


Colon tissue from mice embedded in wax, sectioned, and stained with antibodies. Imaged on fluorescence microscope

Results



Mapt-/- mice display constitutive barrier disruption in the colon and are more susceptible to S. sonnei induced tissue damage but not enteric neuronal loss. H&E stains of a) Control non-Tg B6 mouse colon, b) Control Mapt-/- mouse colon. Arrows indicate loss of barrier integrity. Scale: 50µm. c) Pathology scores of control B6 and Mapt-/- mice colons. d) Pathology scores of B6 and Mapt-/- control and SHIG infected mice mpi. e) Number of enteric neurons in the colon myenteric plexus of B6 and Mapt-/- mice control and SHIG infected 1 mpi. Pink: female. Blue: male.



B6 mice display enteric neuronal loss in the presence of *S. sonnei* infection while Mapt -/- mice exhibit enteric neuronal preservation. Fluorescence microscopy images of a) B6 VEH and SHIG colons stained with TUBB3 antibody (red) showing enteric neurons. Cell nuclei were stained with DAPI (blue). b) Mapt -/- VEH and SHIG colons stained with TUBB3 antibody (red) showing enteric neurons. Cell nuclei were stained with DAPI (blue). Scale: 50 µm

Discussion

- There were clear pathologic morphology disparities between infected wild-type and transgenic mice
- Infected transgenic mice also presented with less enteric neuronal loss than infected wild-type mice
- Our findings suggest infectious disease as a possible driver of neurodegenerative disorders in a tau dependent manner.
- Future studies will be performed to show stronger correlation between enteric neuronal loss and tauopathies

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This project utilizes vertebrate animals as subjects. The protocol for use, "Shigella infections as drivers of neurodegeneration in mice", has been approved by the Institutional Animal Care and Use Committee (IACUC) under the protocol number 21-201079-MC.`