PUBLIC DEFENSE
OF DOCTORAL DISSERTATION
DEPARTMENT OF BIOLOGICAL SCIENCES
GRADUATE PROGRAM

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"UNCOVERING ASTROCYTE ROLES AT THE BLOOD BRAIN BARRIER IN THE HEALTHY AND INJURED BRAIN"

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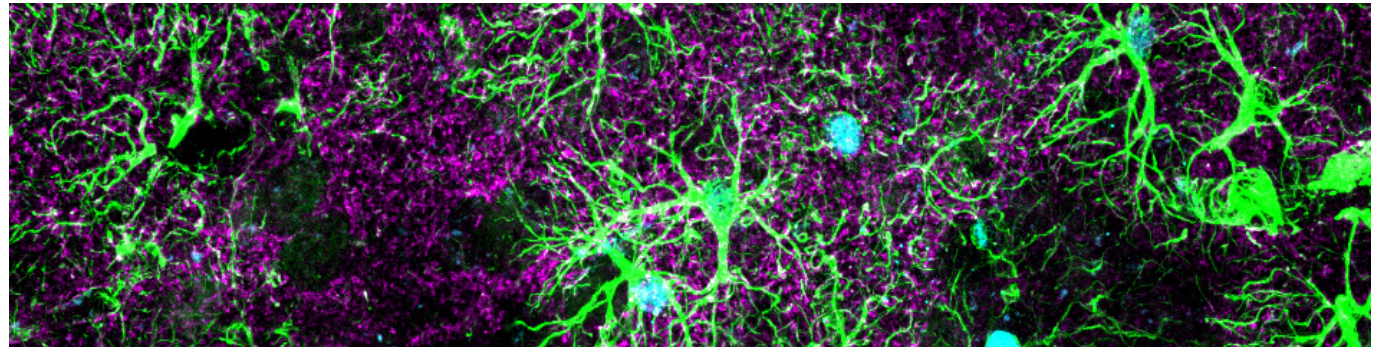
ABSTRACT



The blood-brain barrier (BBB) is regulated by factors that can be secreted by multiple cell types, including astrocytes, that maintain the BBB in health and promote repair after injury. However, astrocyte contributions to the BBB are largely assumed from transplantation studies in which astrocyte progenitor grafts conferred BBB-like properties to tissues that normally lack a BBB. To determine if astrocytes contribute an essential and non-redundant function in maintaining the healthy BBB, we genetically ablated a small number of astrocytes using a conditional, tamoxifen-inducible mouse model. Within 2 hours after induction, we observed sparse astrocyte death in the cortex and leakage of the small molecule Cadaverine and large plasma protein fibrinogen, which are normally contained by a functional BBB. Vessels within regions of ablated astrocyte regions showed reduced expression of the tight junction protein zonula occludens-1, indicating impairment of the physical barrier formed between endothelial cells. Cadaverine leakage persisted for weeks, a feature we also found in mice after mild concussive traumatic brain injury (TBI), thus highlighting the potential for revealing astrocyte roles in post-injury repair. Unlike the genetic ablation model, astrocytes within Cadaverine leakage areas did not undergo cell death after TBI and instead downregulated homeostatic proteins. Our preliminary results show this atypical phenotype appearing 10 minutes after TBI, along with severe vessel rupture, BBB leakage, and disruption of endfoot and basement membrane proteins. This damage persists for months, suggesting that the BBB fails to repair in these areas. Our results provide direct in-vivo evidence for essential astrocyte roles in maintenance of the healthy BBB. Maintenance and/or repair fail after mild concussive TBI, possibly contributing to irreversible progression to neurodegenerative diseases.

BEN HEITHOFF

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  Michael A. Fox, Ph.D. (Co-chair)
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- *HONORS*
  - Outstanding Poster Presentation- Society for Neuroscience, Central Virginia Chapter Virtual Symposium- March 2021
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  - Social Chair, Virginia Tech Roanoke Graduate Student

PRESENTATIONS

Heithoff BP, Robel, S. (March 2021) "Astrocytes are essential for blood-brain barrier maintenance in the adult mouse brain" Poster presentation given at the 2021 Society for Neuroscience, Central Virginia Chapter Virtual Symposium

Heithoff BP, Robel, S. (August 2020) "Astrocytes are essential for blood-brain barrier maintenance in the adult mouse brain" Oral presentation given at the 2020 Virginia Tech School of Neuroscience Summer Research Retreat, Blacksburg, VA

Heithoff BP, George, KK, Phares, AN, Cook DA, Robel, S. (August 2019) "Genetic ablation of astrocytes induces sustained blood-brain barrier dysfunction" Poster presentation given at the 2019 Advancing Neuroscience Research at Virginia Tech Summer Symposium, Blacksburg, VA

Heithoff, BP, Jourdan, LJ, Strauss RE, Gourdie, RG, Robel, S. (March 2018) "Glial fibrillary acidic protein (GFAP) promotes blood-brain barrier function and is protective in mild repeated traumatic brain injury" Poster presentation given at the 2018 Glia in Health and Disease conference, Cold Spring Harbor, NY

Heithoff, BP, Robel, S. (April 2017) "Glial fibrillary acidic protein (GFAP) is protective in mild repeated traumatic brain injury" Poster presentation given at the 2018 American Society for Neurochemistry conference, Little Rock, AK

PUBLICATIONS

"An atypical astrocyte phenotype is responsible for prolonged blood-brain barrier leakage and impairment of repair after mild repeated TBI" **Heithoff, BP**, George KK, Muñoz-Ballester, C Robel, S. In preparation.

"Astrocytes are necessary for blood-brain barrier maintenance in the adult mouse brain." **Heithoff, BP**, George, KK, Phares AN, Zuidhoek, IA, Muñoz-Ballester, C, Robel, S.. *Glia*. Published September 2020, 69 (2), 436-472.

"Repeated Mild/Concussive Traumatic Brain Injury Causes an Atypical Astrocyte Response and Spontaneous Recurrent Seizures." Shandra, O, Winemiller, AR, **Heithoff, BP...** Stefanie Robel. *Journal of Neuroscience*. Published March 2019, 39 (10) 1944-1963.

DEPARTMENT OF BIOLOGICAL SCIENCES GRADUATE PROGRAM

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