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TITLE: Targeting Novel Neurotrophin Effectors for Treating Post-Traumatic Epilepsy

PRINCIPAL INVESTIGATOR: Huaye Zhang

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Piscataway, NJ 08854

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6. AUTHOR(S)
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Traumatic brain injury (TBI) affects about 800,000 children each year and has been linked to various life-long disorders including epilepsy, depression, and intellectual impairment. Despite the prevalence of pediatric TBI, most TBI studies focus on adult animal models. Yet the developing brain exhibits a completely distinctive injury response so it can be difficult to extrapolate the results from adult models to pediatric TBI. Thus, there is an urgent need for research into the effects of pediatric TBI and potential remediation. Neurotrophins are secreted proteins that are important for early brain development and are known to be neuroprotective after injury. However their short biological half-life and poor blood-brain barrier permeability have made it difficult to use neurotrophins in clinical settings. One promising strategy is to target cellular effector proteins of neurotrophins that can be manipulated pharmacologically. Recently, we identified two novel effector proteins within the neurotrophic pathways named Par1 and HuD. These two proteins remain unexplored in TBI research. We found that the levels of these two proteins decrease significantly after pediatric TBI. We also found that both Par1 and HuD are important for brain development and disruption of either protein leads to poor cognitive functions and increased seizure susceptibility, which are symptoms often observed after pediatric TBI. Thus, in this proposal, we will test the molecular and cellular mechanisms by which Par1 and HuD are involved in the pediatric brain injury response, using multifaceted approaches including laser capture and quantitative real time PCR, 3D serial reconstruction, live two-photon in vivo imaging, biochemical and behavioral analyses. We will also use genetic and pharmacological approaches to stimulate the Par1-HuD pathway to determine whether we can promote regeneration and improve behavioral outcomes after pediatric TBI.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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TABLE OF CONTENTS

1. Introduction

Traumatic brain injury (TBI) affects about 800,000 children each year and has been linked to various life-long disorders including epilepsy, depression, and intellectual impairment. Despite the prevalence of pediatric TBI, most TBI studies focus on adult animal models. Yet the developing brain exhibits a completely distinctive injury response so it can be difficult to extrapolate the results from adult models to pediatric TBI. Thus, there is an urgent need for research into the effects of pediatric TBI and potential remediation.

Neurotrophins are secreted proteins that are important for early brain development and are known to be neuroprotective after injury. However their short biological half-life and poor blood-brain barrier permeability have made it difficult to use neurotrophins in clinical settings. One promising strategy is to target cellular effector proteins of neurotrophins that can be manipulated pharmacologically. Recently, we identified two novel effector proteins within the neurotrophic pathways named Par1 and HuD. These two proteins remain unexplored in TBI research. We found that the levels of these two proteins decrease significantly after pediatric TBI. We also found that both Par1 and HuD are important for brain development and disruption of either protein leads to poor cognitive functions and increased seizure susceptibility, which are symptoms often observed after pediatric TBI. Thus, in this proposal, we will test the molecular and cellular mechanisms by which Par1 and HuD are involved in the pediatric brain injury response, using multifaceted approaches including laser capture and quantitative real time PCR, 3D serial reconstruction, live two-photon in vivo imaging, biochemical and behavioral analyses. We will also use genetic and pharmacological approaches to stimulate the Par1-HuD pathway to determine whether we can promote regeneration and improve behavioral outcomes after pediatric TBI.

2. Keywords

Pediatric TBI, Par1, MARK, HuD, neurotrophin

3. Accomplishments

What were the major goals of the project?

Specific Aim 1: To determine Par1 and HuD-dependent molecular, cellular and circuit changes after pediatric TBI.	**Timeline**	**Site 1** (PI)	**Site 2** (co-PI)	**% Completed**
Major Task 1: To analyze Par1 and HuD-dependent expression of key forebrain development molecules	Months			
Subtask 1: Assess molecular markers at P22, P42, and P90 post-TBI and sham surgeries of WT, Par1b KO, and HuD KO mice, using immunohistochemistry and confocal imaging. Participating teams: Dr. Zhang will oversee the immunohistochemistry and confocal imaging, Dr. Crockett will oversee the TBI surgeries.	1-3	Dr. Zhang Dr. Crockett		50%
Subtask 2: Assess molecular markers at P22, P42, and P90 post-TBI and sham surgeries of WT, Par1b KO, and HuD KO mice, using microdissection by laser capture (LCM; MMI) of distinct layers and assessing levels of gene and protein expression by using quantitative real-time PCR (qRT-PCR) and Western blotting Participating teams: Dr. Rasin and Dr. Crockett	2-7		Dr. Rasin Dr. Crockett	50%

Major Task 2: To assess changes in neocortical axonal circuits				
Subtask 1: Perform P21 CHI on transgenic mice that have distinct fluorescently labeled subpopulations of neocortical projection neurons. Participating teams: Dr. Zhang and Dr. Crockett	5-6	Dr. Zhang Dr. Crockett		10%
Subtask 2: Confocal imaging and 3D serial reconstruction of axonal circuits	7-12		Dr. Rasin	10%
Major Task 3: To determine the effect of the Par1-HuD pathway on post-injury recovery of neuronal connectivity in mice subjected to early TBI				
Subtask 1: Analyze pre- and postsynaptic markers at various time points after injury Participating teams: Dr. Zhang will oversee the immunohistochemistry and confocal imaging, Dr. Crockett will oversee the TBI surgeries.	1-3	Dr. Zhang Dr. Crockett		50%
Subtask 2: Perform two photon imaging on mice after P21 TBI. Participating teams: Dr. Zhang and Dr. Crockett	2-12	Dr. Zhang		10%
Specific Aim 2: To determine if acutely inducing Par1 and HuD promotes regeneration and improve behavioral outcomes after pediatric TBI.				
Major Task 4: Effects of genetically inducing Par1 and HuD expression on post-injury recovery				
Subtask 1: Perform E13 in utero electroporation of inducible Par1 or HuD expression vectors Participating teams: Dr. Rasin	12-14		Dr. Rasin	50%
Subtask 2: Analyze circuitry changes using molecular markers and 3D serial reconstruction Participating teams: Dr. Zhang and Dr. Rasin	13-18	Dr. Zhang	Dr. Rasin	50%
Subtask 3: Perform behavioral tests on mice from each experimental condition. Participating teams: Dr. Zhang and Dr. Crockett	13-16	Dr. Zhang Dr. Crockett		0%
Major Task 5: Effects of pharmacologically inducing Par1 and HuD on post-injury recovery				
Subtask 1: Perform two-photon in vivo imaging on injured mice treated with metformin Participating teams: Dr. Zhang and Dr. Crockett	13-24	Dr. Zhang Dr. Crockett		10%
Subtask 2: Examine the effects of metformin on intracortical and subcortical connectivity in injured mice Participating teams: Drs. Rasin and Dr. Crockett	13-24		Dr. Rasin Dr. Crockett	10%
Subtask 3: Examine the effects of metformin on behavioral outcomes of injured mice Participating teams: Drs. Zhang and Dr. Crockett	13-24	Dr. Zhang Dr. Crockett		90%

Milestone #1: Prepare manuscript on Par1 and HuD dependent changes in synaptogenesis and global gene expression changes in mice undergone adolescent TBI. *Participating teams: Drs. Zhang, Rasin, Crockett.*	18-24	Dr. Zhang Dr. Crockett	Dr. Rasin	40%
Specific Aim 3: To determine the role of Par1 in neuroinflammation after pediatric TBI.				
Major Task 6: Role of Par1 in post-injury gliosis and inflammatory cytokine secretion				
Subtask 1: Examine molecular markers of inflammation using Western blot and immunohistochemistry.	25-28	Dr. Zhang		70%
Subtask 2: Examine cytokine profile in WT and Par1b KO mice of different experimental conditions.	31-34	Dr. Zhang		70%
Major Task 7: Examine whether stimulation of Par1 activity can reduce neuroinflammation after TBI				
Subtask 1: Examine molecular markers of inflammation using Western blot and immunohistochemistry after metformin treatment of injured mice	27-30	Dr. Zhang		70%
Subtask 2: Examine cytokine profile in injured mice after metformin treatment.	31-34	Dr. Zhang		30%
Milestone #2: Prepare manuscript on effects of Par1 on neuroinflammation. *Participating teams: Drs. Zhang, Rasin and Crockett.*	30-36	Dr. Zhang Dr. Crockett	Dr. Rasin	90%

What was accomplished under these goals?

1) Major activities
   We have made progress in Major Tasks 1, 3, 5, 6, and 7 listed above.
2) Specific Objectives
   a. Analyze key forebrain development molecules in Par1b KO mice.
   b. Analyze the role of Par1 in post injury gliosis
   c. Examine whether stimulation of Par1 can reduce neuroinflammation and improve behavior.
   d. Perform in utero electroporation with HuD expression vectors and analyze expression of HuD isoforms in the neocortex.

3) Significant results

For Task1 we have begun analysis of key forebrain cortical development and synaptogenesis markers in Par1b WT and KO brains using immunohistochemistry and have identified specific and statistically significant changes of cortical layer and synaptic markers in the Par1b KO brains.

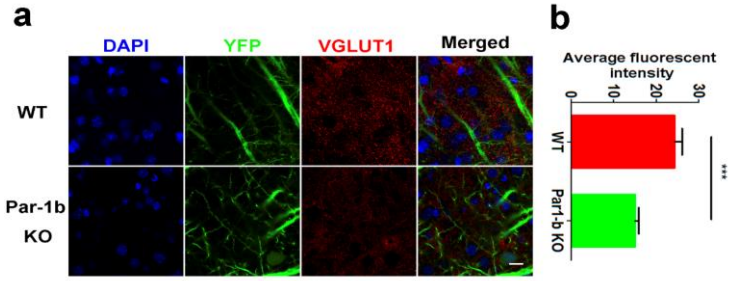


Figure 1. Decreased VGLUT1 Immunoreactivity in The Par-1b/MARK2 Knockout Mice.

a. Representative confocal images of layer V pyramidal neurons (Green) immunostained with DAPI (Blue) and vGluT1 (Red). Par-1b/MARK2 KO mice were crossed with YFP-H mice. Scale bar: 10 µm.
b. Quantification of average fluorescent intensity for each group. Data are shown as mean±SEM, n = 8. ***, p<0.001 by Student's t-test.

We have found that loss of Par1 facilitates microglia activation after injury. The results were quantified and shown to be statistically significant.

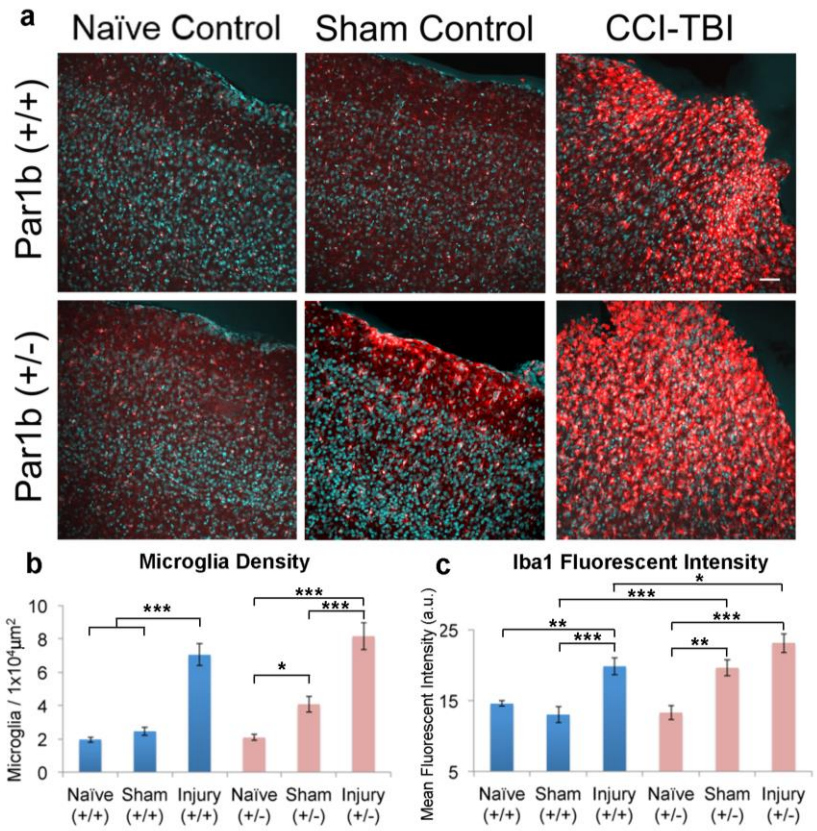


Figure 2: Loss of Par1b increases microglia activation in response to controlled cortical impact injury in mice.
a, Representative 20x confocal images of the parietal association cortex around the impact region in CCI, sham-operated and naïve control Par1b WT (+/+) and Het (+/-) mice 7 days post-surgery. Brains were sectioned and immunostained for microglia marker Iba1 (red) and DAPI (blue). Scale bar = 50 µm. **b,** Quantification of microglial density, n= Par1b (+/+): naïve (5), sham (3), TBI (6); Par1b (+/-):naïve (3), sham (3), TBI (6), *p<0.05, ***p<0.001 by two-way ANOVA. **c,** Quantification of fluorescent intensity of Iba1+ cells, n (animals) = Par1b (+/+): naïve (5), sham (3), TBI (6); Par1b (+/-): naïve (3), sham (3), TBI (6)), *p<0.05, **p<0.01, ***p<0.001 by two-way ANOVA.

We have found that stimulating Par1 with metformin can reduce neuroinflammation and improve behavioral outcomes after TBI. The results were quantified and shown to be statistically significant.

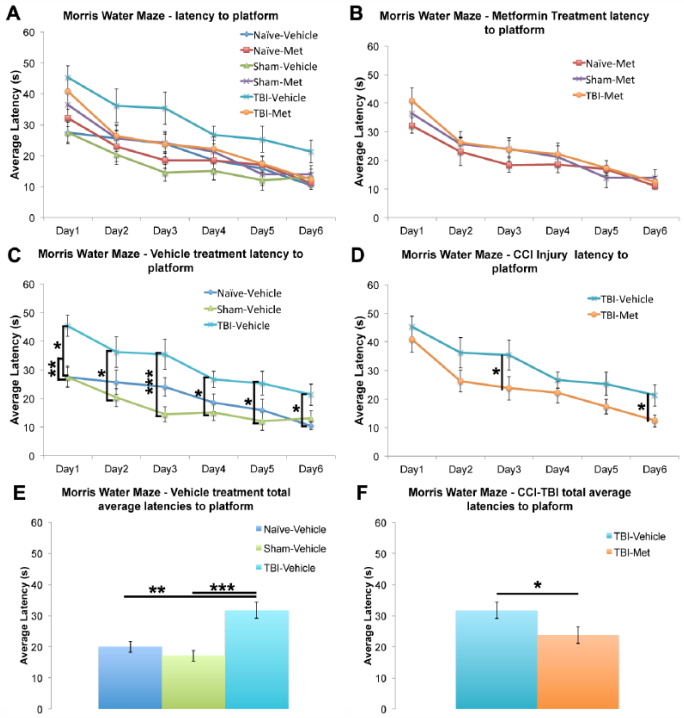


Figure 3. Metformin significantly improved spatial learning following CCI-TBI. Adult CD-1 mice were tested using the Morris Water Maze for six days starting one day post-surgery. The latency for each mouse to find the submerged platform was measured daily (data represent the average of 4 trials per day). **A.** The average latencies for each experimental group were plotted. **B.** Injured mice given metformin were plotted against their sham and naïve controls. No significant difference was observed between different groups. **C.** Injured mice given a vehicle were plotted against their sham and naïve controls. The injured mice consistently performed significantly worse when compared to their sham and naïve controls. **D.** Average latencies for the injured mice treated with either vehicle or metformin. Metformin treated mice performed significantly better than vehicle treated mice as shown by the shorter latency to reach the hidden platform. **E**. The total average latency across all six days for injured mice given a vehicle was plotted against their sham and naïve controls. **F.** The total average latency across all six days for the injured mice treated with either vehicle or metformin. Data represent the mean ± SEM. A 2-way ANOVA was performed with Tukey's post-hoc test, *p<0.05, **p<0.01, ***p<0.001. (Vehicle: N=8, S=12, T=10; Metformin: N=10, S=12, T=11).

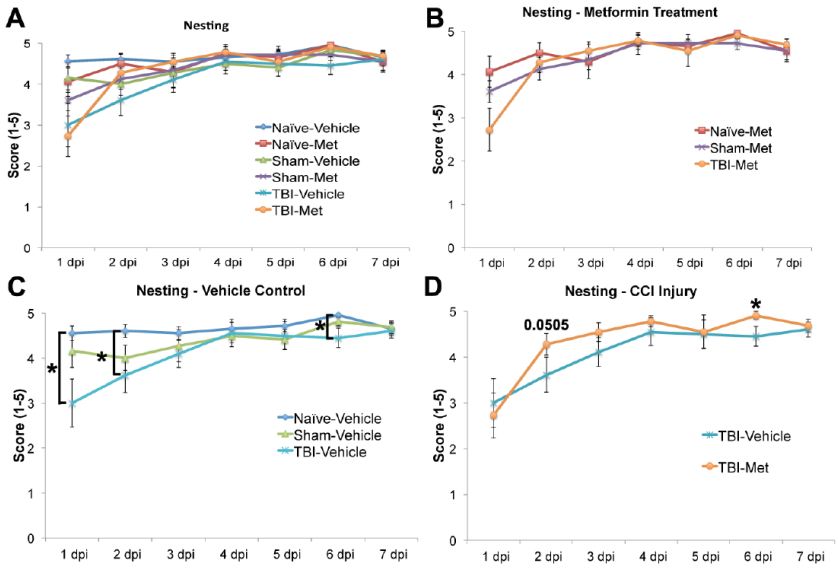


Figure 4. Metformin significantly improved nesting behavior following CCI-TBI. Adult CD-1 mice had their home cage nests ranked each morning starting 1-day post surgery to assess for stress, anxiety, and other emotional disturbances. **A.** The nesting score for the naïve, sham and injured mice treated with either vehicle or metformin were plotted. **B.** Injured mice given metformin were plotted against their sham and naïve controls. No significant differences were found between different groups. **C.** Injured mice given a vehicle were plotted against their sham and naïve controls. Injured mice display significant impairments in nest building as compared to vehicle treated naïve and sham controls. **D.** Injured mice treated with metformin show significantly improved nesting behavior starting the first day post-injury when compared to vehicle treated injured mice. Data represent the mean ± SEM. A 2-way ANOVA was performed with Tukey's post-hoc test, *p<0.05, **p<0.01, ***p<0.001. (Vehicle: N=7, S=10, T=9; Metformin: N=9, S=10, T=8).

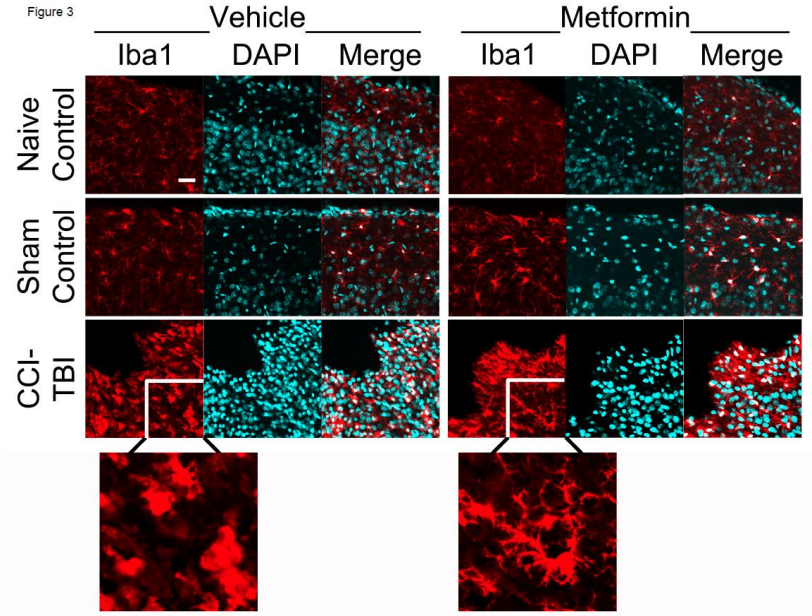


Figure 5. Microglia response following treatment with metformin post-surgery. Naïve, sham-operated control or CCI-TBI mice were treated with either vehicle or metformin beginning at 1-hour post-surgery and daily thereafter. At 7 days post-injury, mice were sacrificed, their brains sectioned and immunostained for microglia marker Iba1 (red) and nuclear marker DAPI (cyan). Confocal images were acquired of the ipsi-lateral cortex for all mouse tissue at 60x. Scale bar = 10μm.

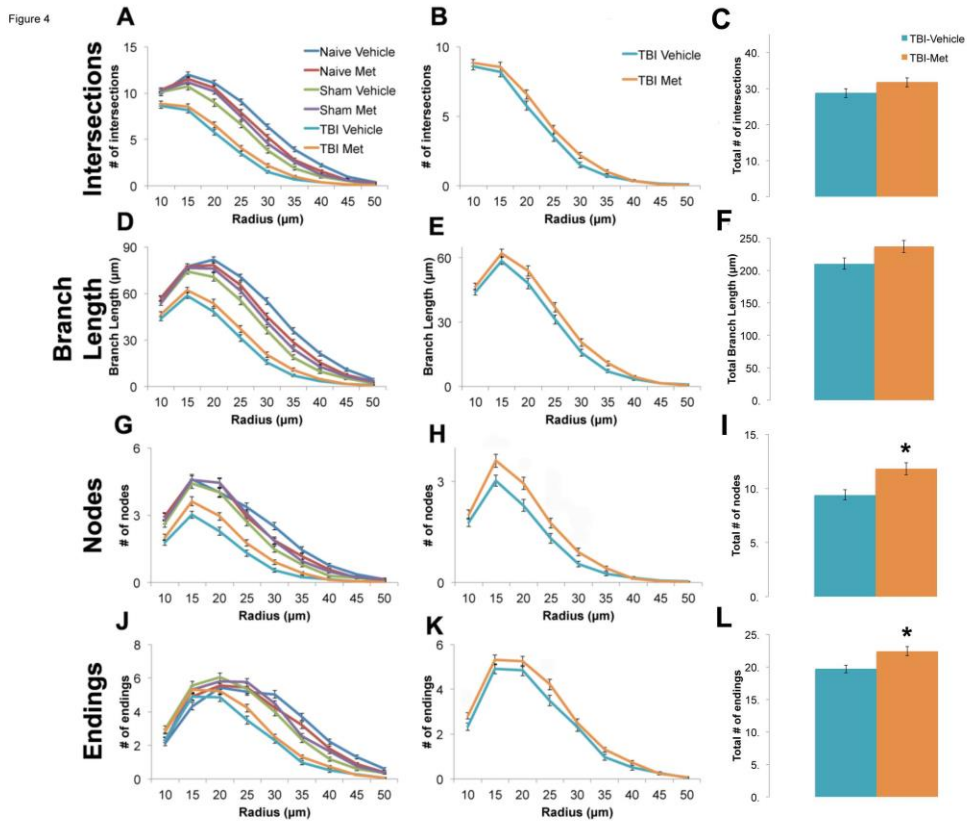


Figure 6. Metformin treatment after injury increased microglia branching complexity. Z-stack images were acquired from the cortex of naïve, sham and CCI-TBI animal tissue treated with either vehicle or metformin. Neurolucida software was used to create 3D reconstructions of individually isolated microglia. Various morphological aspects were measured following Sholl Analysis with a somal radius of 10 μm, including number of intersections (A,B), average branch length (C,D), nodes (E,F), and endings (G,H). Injured mice treated with metformin were found to have significantly more nodes (F) and endings (H) than injured mice treated with vehicle. Data represent the mean ± SEM. A 2-way ANOVA was performed with Bonferroni post-hoc test, *p<0.05. (Vehicle: N=120, S=130, T=120; Metformin: N=120, S=137, T=144).

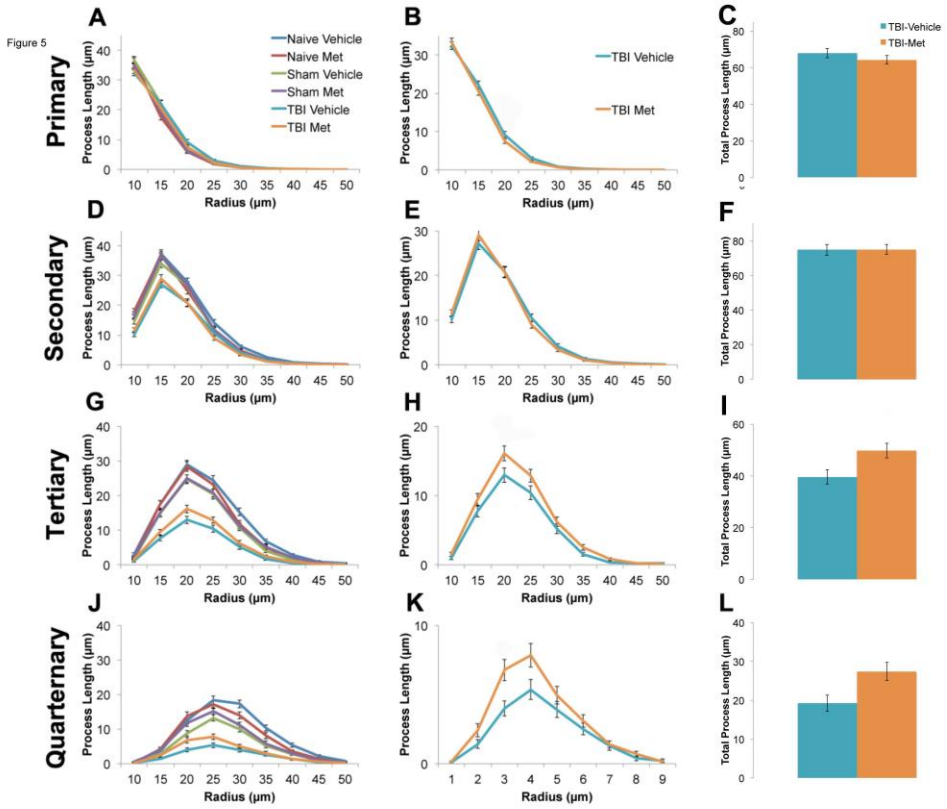


Figure 7. Metformin treatment after injury increased high order branching of microglia. Z-stack images were acquired from the cortex of naïve, sham and CCI-TBI animal tissue treated with either vehicle or metformin. Neurolucida software was used to create 3D reconstructions of individually isolated microglia. Orders of branch complexity was measured following Sholl Analysis with a somal radius of 10 µm, including primary (A,B), secondary (C,D), tertiary (E,F) and quaternary (G,H) orders. Injured mice treated with metformin were found to have higher complexity at the tertiary (F) and quaternary (H) orders than injured mice treated with vehicle. Data represent the mean ± SEM. A 2-way ANOVA was performed with Bonferroni post-hoc test, *p<0.05. (Vehicle: N=120, S=130, T=120; Metformin: N=120, S=137, T=144).

For Task4 we have begun to perform in utero electroporation of HuD expression vectors and analyze the expression of specific HuD isoforms. A better understanding of the role for specific HuD isoforms in neocortical development will help us pinpoint which isoform(s) are responsible for post-traumatic epilepsy after adolescent brain injury.

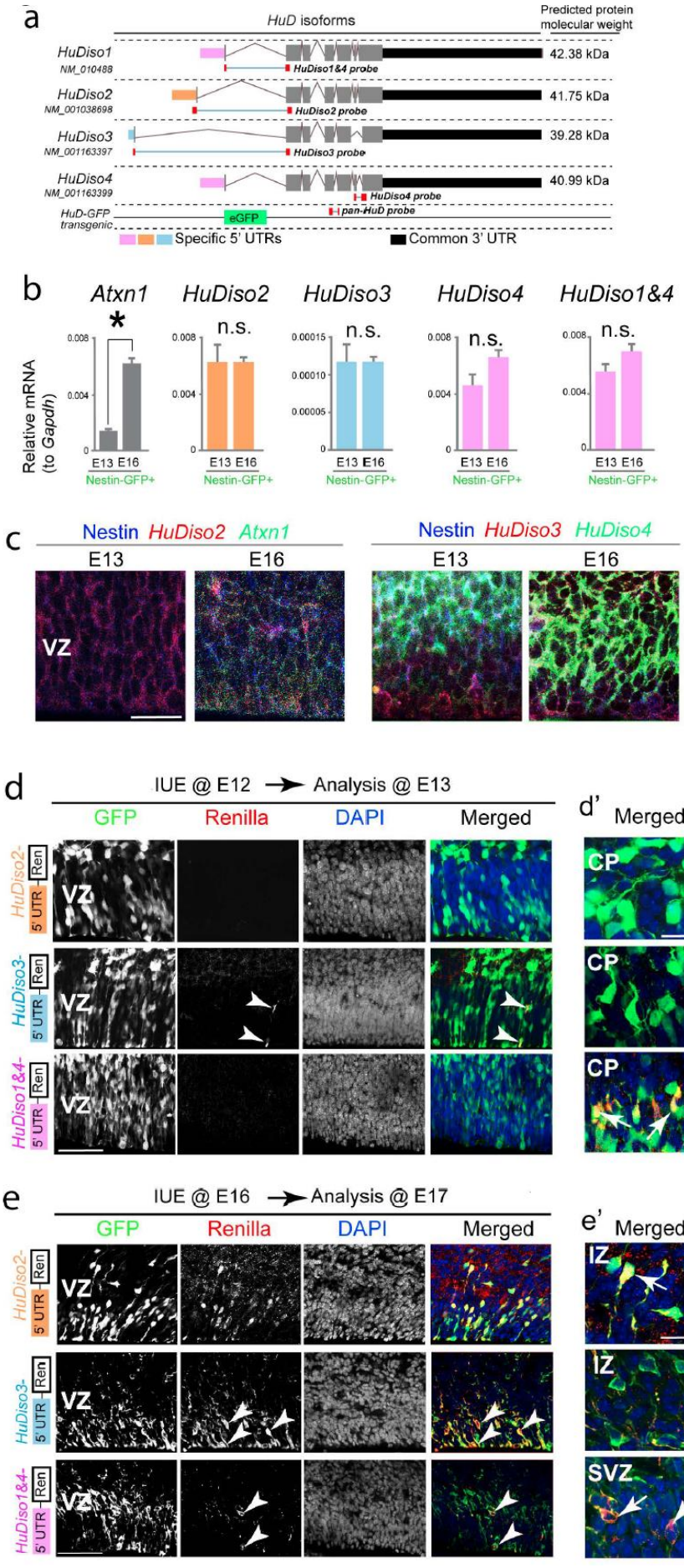
Figure 8

a, Schematic of the four *HuD* isoforms in mice. All isoforms share a common 3' UTR sequence (black). Minor differences are in coding regions (exons in grey) and major differences in 5' UTRs (distinguished by color). NCBI Accession numbers for each variant is indicated underneath common name.

b, Relative mRNA levels of positive control *Atxn1* and the different *HuD* isoforms from FACS-sorted Nestin-GFP+ cells determined by qRT-PCR (n = 3). Data represent the mean and SEM. Data normalized to *Gapdh*. Statistics: Student's t-test. *p < 0.05.

c, Fluorescent *in situ* hybridization of E13 and E16 VZ for *Nestin* (blue), *Atxn1* (green left), *HuDiso2* (red left), *HuDiso3* (red right), and *HuDiso4* (green right). Scale bar: 20 µm.

d and **e,** E13 and E17 neocortices were *in utero* electroporated (IUE) at E12 (**d)** or E16 (**e**). VZ was transfected with CAG-GFP (green) and either *HuDiso2-5' UTR-Renilla, HuDiso3-5' UTR-Renilla* or *HuDiso1&4-5' UTR-Renilla* (red) (n = 3 or 4, respectively). The merged image is far right. Arrowheads represent colocalization in VZ, arrows represent colocalization superficial to VZ. **d'** and **e'** show zoomed-in regions above VZ as indicated. d, e scale bar: 40 µm. d', e' scale bar: 20 µm. IZ = intermediate zone, SVZ = subventricular zone.


a
HuD isoforms
Predicted protein molecular weight
HuDiso1
NM_010488
HuDiso1&4 probe
42.38 kDa
HuDiso2
NM_001038698
HuDiso2 probe
41.75 kDa
HuDiso3
NM_001163397
HuDiso3 probe
39.28 kDa
HuDiso4
NM_001163399
HuDiso4 probe
40.99 kDa
HuD-GFP transgenic
eGFP
pan-HuD probe
Specific 5' UTRs
Common 3' UTR
b
Atxn1
HuDiso2
HuDiso3
HuDiso4
HuDiso1&4
Relative mRNA (to Gapdh)
*
n.s.
E13 E16
Nestin-GFP+
c
Nestin HuDiso2 Atxn1
Nestin HuDiso3 HuDiso4
E13
E16
VZ
d
IUE @ E12 → Analysis @ E13
GFP
Renilla
DAPI
Merged
d' Merged
HuDiso2- 5' UTR Ren
HuDiso3- 5' UTR Ren
HuDiso1&4- 5' UTR Ren
VZ
CP
e
IUE @ E16 → Analysis @ E17
e' Merged
IZ
SVZ

What opportunities for training and professional development has the project provided?

Nothing to report (grant not intended for training and professional development).

How were the results disseminated to communities of interest?

In the current reporting period we have engaged in community outreach activities to enhance public understanding and increase interest in careers in science. First, the PI, Dr. Huaye Zhang, and one of the co-PIs, Dr. Mladen-Roko Rasin, are involved in the Central New Jersey Brain Bee, which has ~80 high school student participants in addition to their siblings, parents and teachers. Dr. Zhang gave a powerpoint presentation at the Brain Bee to discuss the latest neuroscience research and careers in science. Second, the PI and co-PIs organized a booth called "Gray Matters" at the annual Rutgers Day, which attracts nearly 100K visitors to all Rutgers campuses. We discuss with the public about how the brain works through fun games. In addition, we discuss the importance of both preventing TBI and research on TBI therapies.

What do you plan to do during the next reporting period to accomplish the goals?

In the next reporting period, we plan to continue the CHI experiments on P21 mice and analyze molecular markers of forebrain development at different time points after injury, as proposed in Aim 1 of the grant. We will continue our in utero electroporation studies to determine the effects of specific HuD isoforms on post injury recovery, as proposed in Aim 2 of the grant. We have initiated two photon imaging experiments as proposed and will continue with these experiments in the next reporting period.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

Our results so far point to metformin as a potential therapy for TBI. Since metformin has already been used in the clinic for decades and proven to be safe, our results can lead to "drug repurposing" and can potentially be quickly translated into the clinic.

What was the impact on other disciplines?

Our results have identified novel roles for Par1 in microglia activation, which will be of interest to the neuroimmunology field. Further, our results on HuD isoforms can offer insight into the mechanisms of neurodevelopment.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Our results on metformin may lead to new therapies in the clinic for TBI patients.

5. Changes/Problems

No significant changes/problems.

6. Products

Publications, conference papers, and presentations

Journal publications
*DiBona, V.L., Zhu, W., Shah, M., Rafalia, A., Ben Cheikh, H., Crockett, D.P., and **Zhang, H.** Loss of Par1b/MARK2 primes microglia during brain development and enhances their sensitivity to injury. **Journal of Neuroinflammation,** 2019; 16(1):11.*
Status: Published.
Acknowledgement of federal support: Yes.

*DiBona VL, Shah MK, Krause K, Zhu W, Smith D, Crockett DP, and **Zhang H.** Metformin activates the Par1/MARK family kinases and improves cognitive functions after traumatic brain injury.*
*Status: Under revision at **Neuroscience**.*
Acknowledgement of federal support: Yes.

Website(s) or other Internet site(s)
We have submitted our microglia morphology data (included in the Journal of Neuroinflammation publication) to NeuroMorpho.Org, an NIH-sponsored repository for data sharing of morphological data in neuronal and glial cells.

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report.

Other Products
Nothing to report.

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name: *Huaye Zhang*
Project Role: *PI*
Researcher Identifier (e.g. ORCID ID): *0000-0002-4844-6111*
Nearest person month worked: *1*
Contribution to Project: *Supervise project, manuscript writing, editing and submission.*

Name: *Mladen-Roko Rasin*
Project Role: *co-PI*
Researcher Identifier (e.g. ORCID ID): *0000-0003-3063-6096*
Nearest person month worked: *1*
Contribution to Project: *Contribute to data analysis and interpretation of forebrain developmental markers.*

Name: *David Crockett*
Project Role: *co-PI*
Researcher Identifier (e.g. ORCID ID): *0000-0002-8137-755X*
Nearest person month worked: *1*
Contribution to Project: *Contribute to TBI experiments, manuscript editing.*

Name: *Tatiana Popovitchenko*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *12*
Contribution to Project: *IUE experiments, IHC and imaging of forebrain markers*

Name: *Mikayla Voglewede*

Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *5*
Contribution to Project: *TBI experiments, IHC and imaging of forebrain markers*

Name: *Miao Sun*
Project Role: *Research Associate*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *6*
Contribution to Project: *Data analysis on forebrain markers*

Name: *Victoria DiBona*
Project Role: *Postdoctoral fellow*
Researcher Identifier (e.g. ORCID ID): *0000-0002-1914-2506*
Nearest person month worked: *12*
Contribution to Project: *Analysis of effects of Par1 on neuroinflammation and the effect of metformin on injury recovery.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Zhang, Huaye

R21 AG063123 04/15/19-12/31/20 1.2 calendar months
NIH/NIA ADC: $150,000 Total: $437,250
Role: PI
Title: Polarity determinants in endolysosomal trafficking and proteostasis: Implications for Alzheimer's disease pathogenesis
Overlap: None

Pilot Grant 01/01/19-12/31/19 0.6 calendar months
Rutgers BHI ADC: $40,000 Total: $40,000
Role: co-I (PI: Alexander Kusnecov)
Title: Maternal T cell activation during pregnancy and postnatal neurobehavioral development
The goal of this internal pilot grant from the Rutgers Brain Health Institute is to investigate the impact of the maternal immune response to the T cell superantigen (SAg), staphylococcal enterotoxin A (SEA), on postnatal changes in offspring behavior, microglial cell function, and dendritic spine plasticity.
Overlap: None

What other organizations were involved as partners?
Nothing to report.

8. Special Reporting Requirements

Quad Chart: Updated Quad Chart attached.

9. Appendices