

Brain biomarker profiles vary with semi-synthetic and grain-based diets in healthy and mTBI mice

Erin D. Anderson^{a,✉}, Daunel V. Augustin^a, Anastasia P. Georges^a, David A. Issadore^{a,b}, David F. Meaney^{a,c,*}

^a Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, United States

^b Department of Electrical and Systems Engineering, University of Pennsylvania, Philadelphia, PA 19104, United States

^c Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA 19104, United States

ARTICLE INFO

Keywords:

mTBI
Diet
Biomarkers

ABSTRACT

Across a range of neurological disorders, there is a growing appreciation for how the gut influences brain health, but few ways of monitoring its effects. Although nutrition influences traumatic brain injury (TBI) recovery, its influence on biomarkers—whether as an intervention or confounder—is poorly understood. Beyond specialized diets, standard rodent diets may also affect brain function. Neuron-derived extracellular vesicles (NDEVs) offer a brain-specific complement to circulating biomarkers, but their sensitivity to diet is unknown. In this study, we isolated miRNAs from NDEVs from the serum of healthy and mild TBI (mTBI) mice fed a semi-synthetic or grain-based diet. NDEV miRNAs encoded dietary differences based on injury condition, suggesting that NDEVs are sensitive to dietary changes and may be able to track diet's effect on TBI recovery. Additionally, we found that diet influenced injury biomarkers, underscoring diet as a confounding variable for NDEV miRNA biomarkers. Together, these findings highlight NDEVs as a promising tool for monitoring the effects of subtle dietary differences on brain health and the importance of diet reporting to improve study reproducibility.

1. Introduction

For moderate-to-severe traumatic brain injury (TBI), protein biomarkers aid in diagnosis and prognosis, but for mild TBI (mTBI), a persistent challenge is balancing the relative mildness of the injury with confounding factors [1]. In particular, diet, age, sex, polytrauma, and exposure history affect the efficacy of common TBI biomarkers including GFAP, UCHL1, t-tau, NfL, and S100B [2]. Circulating miRNAs and extracellular vesicle (EV) encapsulated miRNAs are emerging biomarker classes that may be more sensitive to mTBI, as in cancer [3]. Unlike protein biomarkers, miRNA biomarkers' robustness to biological, environmental, and dietary factors is not well characterized.

There is an emerging appreciation for how diet composition and dietary supplements affect TBI recovery, but less is known about how they affect brain biomarkers. In the gut, TBI induces systemic inflammation, gut dysbiosis, and mucosal barrier dysfunction [4]. TBI recovery is particularly sensitive to dietary fat content through changes in inflammation, plasma membrane permeability, and oxidative stress [5].

Moreover, dietary supplements (omega-3 fatty acids and vitamin D) influence TBI biomarkers [6] and diet itself has far-ranging effects on miRNA expression [7] and circulating neurological disease biomarkers (e.g., [8,9]).

Beyond specialized diets and supplementation, differences among standard diets also contribute to differences in gut health, affecting body weight/composition, blood glucose, and gut microbiome diversity [10,11]. Despite calls to report rodent diet selection [12], little is known about how that selection influences neurological disease.

We sought to understand whether standard diet selection affects mTBI biomarkers. In this study, we used track-etched nanopore (TENPO) technology to isolate miRNAs from neuron-derived extracellular vesicles from mice fed semi-synthetic or grain-based diet and then subjected to mTBI, allowing us sufficient specificity and sensitivity to study small, but significant, effects. We examined how diet affects miRNA expression and influences mTBI biomarker identification and generalization. This study calls attention to an often-overlooked experimental factor influencing biomarker reproducibility.

* Corresponding author at: Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, United States.

E-mail addresses: anderin@seas.upenn.edu (E.D. Anderson), daunelaugustin@gmail.com (D.V. Augustin), ageorges@seas.upenn.edu (A.P. Georges), issadore@seas.upenn.edu (D.A. Issadore), dmeaney@seas.upenn.edu (D.F. Meaney).

<https://doi.org/10.1016/j.neulet.2025.138318>

Received 7 May 2025; Received in revised form 11 July 2025; Accepted 14 July 2025

Available online 14 July 2025

0304-3940/© 2025 Published by Elsevier B.V.

2. Methods

2.1. Animals

C57BL/6 mice (8–12 weeks old; male; Charles River Laboratories) were socially housed 5 mice/cage with a 12 h light/dark cycle and ad libitum food and water. We used 87 total mice. This study was approved by the University of Pennsylvania's Animal Care and Use Committee.

2.2. Closed-head controlled cortical impact

To administer mild traumatic brain injury (mTBI), we followed previously established protocols [13]. We initiated anesthesia with 3.5 % isoflurane in oxygen and maintained it at 1.5–2 %. After confirming anesthesia depth, we made a 1-cm incision on the mouse's scalp to expose the skull for sham and mTBI mice. For mTBI mice, we used the Impact One Stereotactic Impactor (Leica) fitted with a 6-mm rubber tip to administer a 3.5-m/s impact with 1-mm impact depth and 30-ms dwell time over the left parietal bone, excluding mice for skull fracture. We then sutured the scalp closed and placed the mouse in a heated recovery cage until it exhibited normal alertness and ambulation before returning it to the colony.

2.3. Diet regimen

This study used two diet formulations: grain-based Laboratory Diet 5001 (Animal Specialties and Provisions) and semi-synthetic AIN-76A (Research Diets). Upon arrival, all mice were fed grain-based diet. Ten days prior to sham or mTBI surgery, mice were fed either grain-based ($N = 27$ sham; $N = 28$ mTBI) or semi-synthetic diet ($N = 16$ sham; $N = 16$ mTBI). Given the possibility that diet and mTBI could both affect neuron-derived extracellular vesicle (NDEV) cargo, we focused our design on whether diet differences prior to injury would have long-lasting effects on NDEV biomarkers during injury recovery. Therefore, we simplified our design, and post-surgery, returned all mice to grain-based diet. Mice with fighting-related skin lesions were excluded.

2.4. Serum collection

We euthanized mice with a lethal dose (250 mg/kg) of sodium pentobarbital and collected whole blood via cardiac puncture. The blood coagulated at room temperature for 30–60 min before centrifugation at 433xg for 15 min at 4°C to isolate serum. We stored serum at –80°C before processing.

2.5. Neuron-derived extracellular vesicle isolation

We used Track-Etched NanoPore (TENPO) technology with 3 μ m pores to isolate GluR2 + extracellular vesicles (EVs) as previously described [14–16]. TENPO was selected for its higher specificity for neuron-derived EVs via surface marker capture, and its ability to minimize contamination from background EVs and non-EV nanoparticles, which was necessary to accurately assess diet-induced changes [14–16]. We pooled serum from 2 to 3 mice per sample to form 500 μ L serum samples with $N = 10$ (sham-grain), $N = 9$ (mTBI-grain), and $N = 8$ (sham-synthetic; mTBI-synthetic) as previously described [17]. Pooling was necessary for consistent chip performance and downstream RNA extraction efficiency, allowing us to measure weakly expressed markers in response to mild injury and diet. We lysed EVs on chip using QIAzol (Qiagen) to enrich for RNAs.

2.6. miRNA isolation & sequencing

We purified miRNAs using the miRNeasy Kit (Qiagen), and generated a miRNA library for sequencing using the QIAseq miRNA Library Kit (Qiagen). We sequenced using the NovaSeq 6000 SP Kit (Illumina; Next-

Generation Sequencing Core, University of Pennsylvania). We demultiplexed and aligned the FASTQ files to the *Mus musculus* genome using Qiagen's GeneGlobe Analysis Portal and exported the expression matrices to RStudio.

2.7. Differential gene expression

We used DESeq2 (v1.44.0) for R (v4.4.1) to normalize read counts. We excluded samples that failed library preparation and had a total read count < 10 across all miRNAs, and excluded miRNAs with an average read count < 1/sample. For semi-synthetic diet miRNAs, we reanalyzed data presented in [17].

2.8. Functional enrichment analysis

We identified enriched pathways using miRNet v2.0. We matched miRNAs to target genes in miRTarBase v8.0 and pathways in the Kyoto Encyclopedia of Genes and Genomes (KEGG). We performed a hypergeometric test to identify significantly enriched genes and their corresponding pathways with false-discovery rate < 0.1.

2.9. Statistical analysis

Data are presented as mean $\pm$ standard error (SE). Wald's Test was used for differential expression analysis. We corrected for multiple comparisons using false-discovery rate. We used logistic regression to classify mTBI and derive AUCs, and used DeLong's Test to compare AUCs. Statistical analysis was performed using R (v4.4.1). Data were plotted using GraphPad Prism v10.4.0.

3. Results

Using TENPO technology (Fig. 1A), we identified five differentially expressed miRNAs from neuron-derived EVs relating to grain-based or semi-synthetic diet. miR-151-3p was differentially expressed regardless of injury condition (Fig. 1B; $\log_2$ fold change ($\log_2$ FC) $\pm$ SE = 1.0 ± 0.3 (sham) and 1.1 ± 0.4 (mTBI)), miR-7a-5p and miR-184-3p were differentially expressed in sham only (Fig. 1C-D; $\log_2$ FC $\pm$ SE = -0.9 ± 0.3 and 2.2 ± 0.8 , respectively), and miR-8117 and miR-340-5p were differentially expressed in mTBI only (Fig. 1E-F; $\log_2$ FC $\pm$ SE = -1.9 ± 0.6 and 0.9 ± 0.2 , respectively); diet modifies EV content based on injury. We then considered the pathways those miRNAs regulated: the aggregate miRNAs associated with diet differences for sham (miR-151-3p, miR-7a-5p, miR-184-3p) versus mTBI (miR-151-3p, miR-8117, miR-340-5p). Pathways common to sham and mTBI were related to oxygen homeostasis and circadian rhythms, whereas those related to sham were predominantly associated with insulin, blood pressure and sodium levels, and diabetes (Fig. 1G). mTBI pathways were related to a range of factors, including axonal growth and guidance, vascular and epithelial integrity, and cell division (Fig. 1G).

Next, we identified mTBI biomarkers based on diet and evaluated their generalizability. miR-203-3p and miR-122-5p were differentially expressed by mice fed semi-synthetic diets (Fig. 2A-B; $\log_2$ FC $\pm$ SE = -1.7 ± 0.5 and 1.5 ± 0.4 , respectively) and miR-8117 was differentially expressed for grain-based diet (Fig. 2C; $\log_2$ FC $\pm$ SE = -1.8 ± 0.6). We trained logistic regression models to distinguish sham from mTBI based on semi-synthetic (miR-203-3p and miR-122-5p) or grain-derived (miR-8117) diet, and evaluated their performance in the training set (diet used to train the model), and in the testing set (diet *not* used to train the model) (Fig. 2D). Each of the three miRNAs distinguished sham from mTBI in the training set with high AUC (AUC > 0.75), but only miR-122-5p and miR-8117 were superior to random guessing (95 % CI [0.55,1] and [0.53,1], respectively; Fig. 2D). However, none of the differentially expressed miRNAs generalized to the alternative diet; none were significantly better than random guessing (Fig. 2D).

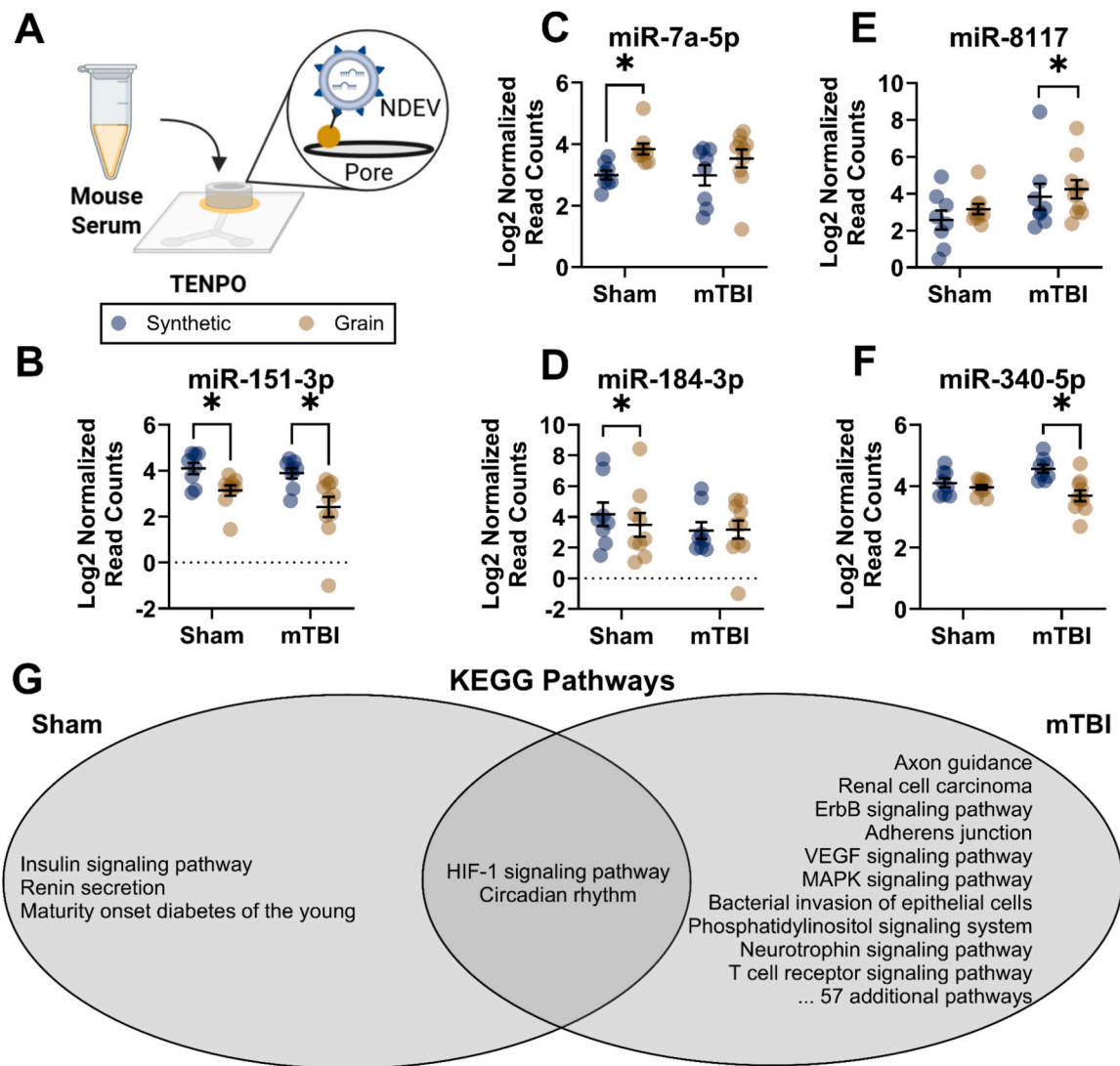


Fig. 1. Diet affects miRNAs from neuron-derived extracellular vesicles in sham and mTBI mice. (A) TENPO for isolating NDEVs from serum (BioRender). (B-F) miRNAs differentially expressed based on diet. (G) KEGG Pathways for differentially expressed miRNAs. * indicates $q < 0.1$.

4. Discussion

In this study, we considered how standard rodent diets influence the brain's molecular fingerprint at baseline and in mild traumatic brain injury (mTBI). We found that diet produced injury-dependent and -independent changes in miRNAs from neuron-derived extracellular vesicles (NDEVs). Moreover, we found that injury biomarkers depended on diet selection and did not generalize well between diets. This study highlights how diet can influence brain biomarker presentation, with implications across neurological conditions.

Emerging studies are beginning to understand how standard rodent diets affect gut and brain health. Semi-synthetic diets, such as AIN-76A and AIN-93, have consistent and well-defined nutritional composition relative to grain-based diets, which have diverse grain and protein sources and variable nutritional content [12]. AIN-76A specifically has high sucrose content, which can contribute to glucose intolerance and insulin dysfunction [12], as we observed through pathway analysis. Grain-based diets contain increased soluble fiber, which is fermented into short-chain fatty acids (SCFAs) [11], whereas semi-synthetic diets rely on less-fermentable cellulose for fiber [11]. SCFAs play a key role in systemic inflammation [18], and TBI reduces fecal SCFAs, while dietary SCFA supplementation improves TBI recovery [19]. Furthermore, semi-synthetic diets affect kynurenine pathway metabolites, which connect

the immune and nervous systems, and are affected by TBI [20]. Our prior work defined neuroimmunity's central role in postacute mTBI biomarkers [17], and, in the present work, diet selection affected miR-151-3p, miR-8117, and miR-340-5p in mTBI mice, producing potentially neuroimmune effects evidenced by the associated pathways, including neurotrophin, T-cell receptor, MAPK, and ErbB signaling.

A challenge in identifying biomarkers for dietary intervention and neurological disease is brain specificity: many markers of metabolic dysfunction or inflammation cannot be causally linked to the brain [21]. For example, although high fat diets increase nonspecific markers of inflammation (MCP-1) and exacerbate TBI's cognitive deficits [22], identifying a pharmacological target is less obvious. Here, we leveraged NDEVs to gain neuronal specificity. For semi-synthetic diet, miR-203-3p and miR-122-5p differentiated mTBI and sham mice. miR-203-3p was previously identified as a diagnostic biomarker for TBI [15,17], and contributes to regulation of neuroinflammation [23]. Similarly, miR-122-5p is upregulated in neurological disease and is involved in neuronal apoptosis and neuroinflammation [24]. miR-8117, which differentiated sham from mTBI in grain-fed mice, is downregulated in microglial EVs associated with postoperative pain [25]. Despite the lack of generalizability in the specific miRNA biomarkers we identified, they share neuroimmune mechanisms. Together, these results emphasize the potential importance of using neuroimmune miRNAs in brain-health

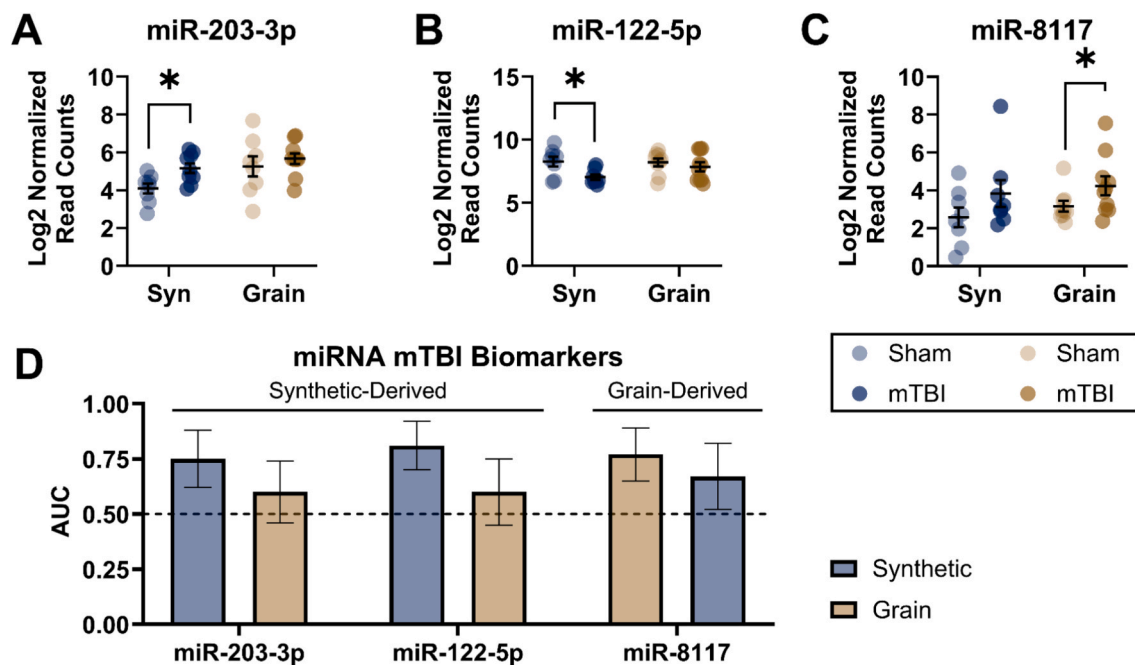


Fig. 2. Diet affects identification and efficacy of mTBI biomarkers. Neuron-derived EV miRNAs differentially expressed based on head injury exposure fed the (A-B) semi-synthetic diet and (C) grain-based diet. (D) AUCs for injury-dependent miRNAs across diets. * indicates $q < 0.1$.

management post-TBI.

Given that diet is often considered a predisposing factor or even a treatment for neurological disease [2,5], we explored if diet-related biomarker differences were accompanied by diet-related neurocognitive differences. We found no significant difference in novelty memory or open field exploration based on diet in either injury condition (data not shown). We did, however, observe that mice fed semi-synthetic diet exhibited increased aggression and fighting with their cagemates relative to grain-fed mice, despite identical housing, environmental conditions, and distribution of injury conditions within a cage. The extent this aggressive social phenotype could influence miRNA expression in NDEVs is not clear, but these observations suggest that future studies should consider social interactions and cognitive function as additional measures to correlate with NDEV content.

In this work, we used neuron-derived extracellular vesicles to isolate the effects of diet on neuronal signaling with and without brain injury. We find it is both important to consider diet as a confounding factor for TBI biomarkers and that NDEVs provide an opportunity to surveil and mechanistically understand how diet affects the brain.

CRedit authorship contribution statement

Erin D. Anderson: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Daunel V. Augustin:** Methodology, Investigation, Data curation. **Anastasia P. Georges:** Project administration, Methodology. **David A. Issadore:** Writing – review & editing, Supervision, Methodology. **David F. Meaney:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Significance statement

Our study shows that rodent diet composition prior to injury significantly changes the miRNAs in neuronal extracellular vesicles in the postacute phase of traumatic brain injury.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Our work was supported by the Paul G. Allen Frontiers Group Grant 12347, and NIH R01 NS135406.

Data availability

Data will be made available on request.

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