Introduction

Traumatic brain injury (TBI) is a condition often identified among Veterans deployed to the Persian Gulf region in support of Operation Enduring Freedom (OEF) or Operation Iraqi Freedom (OIF). TBI is caused by one or more concussive insults to the head or a penetrating head injury that disrupts the normal functions of the brain, leading to either transient or chronic impairments in physical, cognitive, emotional and behavioral functions [1-6]. In OEF/OIF Veterans, TBI is largely the result of concussive injuries from blast-producing weaponry [7]. Veterans exposed to blasts from prior conflicts have shown evidence of mild TBI (mTBI) and attention difficulties when compared to similar Veterans without blast exposure. Mild TBI can be difficult to diagnose and, when coupled with psychological illness, can be either misdiagnosed or missed altogether. Traditionally, physicians and scientists have viewed and interpreted diseases at the ‘visual’ clinical level. However, with the advent of genomics and proteomics technologies, personalized medicine offers the promise and potential of uncovering the largely ‘unseen’ details of disease causality, onset, and progression.

New evidence has highlighted defects in neural
circuits and synapses, and the plastic processes controlling these functions, in TBI [8-13]. While gene products relevant to these processes are expressed in the brain, some of these genes are also expressed in circulating blood cells, such as peripheral blood mononuclear cells (PBMCs) [14-17]. Consistent with this, recent studies have illustrated that PBMC-associated biomarkers may provide insights into the pathogenesis of neurological disorders such as Alzheimer’s disease and may be used to monitor disease diagnosis and progression [18,19]. Thus, PBMCs may also provide an ideal clinically accessible “window” into the brain, reflecting molecular alterations following TBI which might contribute to the onset and progression of clinical TBI phenotypes.

Small non-coding RNAs, including microRNA (miRNA) and small nucleolar RNA (snoRNA), are increasingly recognized for their roles in the regulation of cellular processes in health and disease [20]. Select small non-coding RNAs, particularly miRNA, have been implicated in neurological disorders [21-23]. It is possible that miRNA and other small non-coding RNAs might contribute to the onset and/or progression of clinical complications following TBI [24]. Exploring the feasibility of identifying clinically accessible TBI biomarkers, we identified select small non-coding RNA fingerprints from clinically accessible PBMCs that may be used as independent biological indexes of mTBI in OEF/OIF Veterans. Outcomes from our studies suggest that additional applications of the clinically accessible small non-coding RNA biomarkers to current diagnostic criteria may lead to improved mTBI detection and more sensitive outcome measures for clinical trials.

Materials and methods

18 OIF and OEF Veterans (9 mTBI and 9 non-mTBI control cases) were recruited by The War Related Illness and Injury Study Center (WRIISC), Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS), East Orange, NJ. Male and female participants were included if they were between 18-75 years of age and completed a clinic al evaluation at the New Jersey WRIISC. Participants were included regardless of their mTBI history. Cases with inter-current infections or inflammatory-related conditions were excluded. Participants were classified as having a history of mTBI if they positively endorsed at least one of 4 items on the Veteran traumatic brain injury screening tool (VAT-BIST) [25] and had a score at least one standard deviation below the norm for age and education on the Repeatable Battery for Neuropsychological Testing (RBANS) [26]. Classification criteria for Control cases included a negative VAT-BIST score and a RBANS score less than one standard deviation below the norm.

Demographic information for individual mTBI and non-mTBI cases is presented in Table 1. The average age of mTBI and non-mTBI cases used in our interim Biomarker Discovery study was, respectively, 31.6±7.0 and 29.8±8.2 years. The interval between Veterans’ last deployment and recruitment into this study was 3.9±2.7 and 2.6±2.1 years for the mTBI and non-mTBI group, respectively. The mTBI group had an average of 13.3±1.3 years of education and the non-mTBI group had an average 13.0±2.4 years of education. There was no significant difference in age, deployment interval or years of education between the mTBI and the non-mTBI groups (t-test assessments of mTBI versus non-mTBI groups: p-values of 0.59 for age, 0.30 for deployment interval, and 0.72 for duration of education). The proportion of males in the mTBI and the non-mTBI group was, respectively, 78% and 67%. Lastly, 89% of the mTBI veteran cases used in our study were co-morbid with post-traumatic stress disorder (PTSD), based on a PTSD diagnosis criterion of having a score of 50 or more in the PTSD Checklist - Civilian Version [27]. Thus non-mTBI cases were selected to match for PTSD, with 78% of cases in the non-mTBI control group diagnosed with PTSD.

PBMC isolation

Blood specimens were collected by venipuncture and drawn into BD Vacutainer CPT Cell Preparation Tubes. PBMCs were isolated from freshly collected blood specimens following manufacturer’s instructions (Becton, Dickinson and Company) and were stored at -80 °C until use.

RNA preparation and high throughput analysis of small non-coding RNAs

Total RNA was isolated from approximately 10-50 mg of PBMCs using RNA STAT-60 according to the manufacturer’s instructions (Tel-Test,
Biological surrogates for distinguishing TBI from PTSD

Friendswood, TX, USA). Immediately prior to RNA labeling, the purity and concentration of RNA samples were determined from OD260/280 readings using a dual beam UV spectrophotometer and RNA integrity was determined by capillary electrophoresis using the RNA 6000 Nano Lab-on-a-Chip kit and the Bioanalyzer 2100 (Agilent Technologies, Santa Clara, CA, USA) as per the manufacturer’s instructions. Total RNA was directly modified and labeled using the FlashTag™ HSR Biotin RNA Labeling Kit according to the manufacturer’s instructions (Genisphere, Hatfield, PA). Verification of biotin labeling was obtained by an enzyme-linked oligoabsorbant assay (ELOSA) using Immobilizer™ Amino – 8 well strips (Nunc/Thermo Fisher Scientific, Rochester, NY, USA) according to instructions supplied by Genisphere. Labeled cRNA

Table 1. Demographic characteristics of mTBI and non-mTBI control cases we used in our interim Biomarker Discovery study. Mild TBI classification is based on positive endorsement of the VA traumatic brain injury screen (VAT-BIS) and a score of at least one standard deviation below the norm for age and education on the Repeatable Battery for Neuropsychological Testing (RBANS). Non-mTBI case classification is based on negative endorsement of VAT-BIS and a RBANS score of less than one standard deviation below the norm. PTSD diagnosis is based on a score of 50 or more on the PTSD Checklist – Civilian Version. Average age: mTBI group, 31.6±7.0 yrs; non-mTBI group, 29.8±8.2 yrs. Interval between their last deployment and recruitment into this study: mTBI group, 3.9±2.7 yrs; non-mTBI group 2.6±2.1 yrs. Average duration of education: mTBI group, 13.3±1.3; non-mTBI group, 13.0±2.4 yrs. Percentage of males: mTBI group, 78%; non-mTBI group, 67%. Percent of cases with co-morbid PTSD: mTBI group, 89%; non-mTBI group, 78%.

<table>
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<th>Case</th>
<th>mTBI/Ctl</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Interval (yrs) since last deployment</th>
<th>Education (yrs)</th>
<th>Comorbidity PTSD</th>
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<td>31529</td>
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<td>38</td>
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<tr>
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<tr>
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<tr>
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<td>Black, non-Hispanic</td>
<td>1.0</td>
<td>12</td>
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</tr>
</tbody>
</table>
(1.0 μg) was hybridized for 16 hr at 48°C to Affymetrix microRNA v.1.0 arrays (Affymetrix, Santa Clara, CA, USA), which contain probe sets for 1,500 small non-coding RNAs, including microRNA (miRNA), small nuclear RNA (snRNA), small Cajal body-specific RNA ( scaRNA), and 5.8S ribosomal RNA (rRNA). Array content was derived from the Sanger miRBase miRNA database v11 (April 15, 2008, http://microrna.sanger.ac.uk), snoRNABase (www.snorna.biotoul.fr) and the Ensembl Archive (www.ensembl.org). Arrays were washed and stained on a Fluidics Station 450 (Affymetrix) according to the manufacturer’s recommended procedures. The arrays were stained with phycoerythrin-conjugated streptavidin (Invitrogen/Life Technologies, Carlsbad, CA, USA) and the fluorescence intensities determined using a GCS 3000 7G high-resolution confocal laser scanner and AGCC software (Affymetrix). The scanned images were analyzed with the miRNA QC tool (Affymetrix) using RMA global background correction, quantile normalization and median polish summarization to generate quantified data (as recommended by Genisphere). Quality control metrics for arrays included normalized signal values > 1000 for five spike-in control oligo probe sets (Genisphere).

Small RNA probe sets exhibiting significant differential expression (SDE) were identified using the following steps in GeneMaths XT (Applied Maths, Austin TX): 1) Probed sets with array detection p-values ≤ 0.05 for all samples in at least one experimental group were selected for further analysis, 2) Performed Discriminant Analysis (DA) and determined the largest percentage of remaining probe sets that permitted correct group assignment of samples in unsupervised hierarchical clustering by the Unweighted Pair-Group Method using Arithmetic Averages (UPGMA) based on cosine correlation of row mean centered log2 signal values; this was the top 50%-tile, 3) In the DA top 50%-tile, selected probe sets with absolute signal log2 fold changes ≥ 1.0 and independent t-test p-values ≤ 0.05 adjusted for multiple testing error by the Benjamini-Hochberg false-discovery rate (FDR) correction method [28]. Unsupervised hierarchical clustering of probes sets and heat map generation were performed in GeneMaths XT following row mean centering of log2 transformed MAS5.0 signal values; probe set clustering was performed by the UPGMA method using Cosine correlation as the similarity metric. For comparative purposes, clustered heat maps included probe sets for spike-in controls (Genisphere), or endogenous small RNAs exhibiting: 1) Array detection p-values ≤ 0.05, and 2) either a) a log2 signal value standard deviation ≤ 0.025 for all samples or b) in the DA top 50%-tile with an FC > 1.3 in the opposite direction of the selected SDE profile.

Confirmatory quantitative Real-Time Polymerase Chain Reaction (qPCR) studies

We identified specific target sequences for each of the 18 candidate small RNA biomarkers (Table 2). Based on the sequence information, qPCR primer sets specific for each of the biomarkers were custom-designed and synthesized commercially by Applied Biosystems (Carlsbad, CA). One microgram of total RNA was used to prepare complementary DNA (cDNA) libraries using the High-Capacity cDNA Archive Kit (Applied Biosystems, Foster City, California) in a total volume of 20 μL. Data were normalized relative to those for the 58S ribosomal RNA. Levels of targeted small non-coding RNA were expressed relative to those in control groups using the $2^{-\Delta\Delta C_{t}}$ method [29].

Results

Using the Affymetrix Human Gene 1.0 ST Array chip as a high-throughput platform, we analyzed the expression profile of 1500 small non-coding RNAs in our human PBMC specimens from the mTBI and non-mTBI cases in our OEF/OIF Veteran study cohort. We detected a total of 428 small RNA species from our PBMC specimens: 190 miRNAs, 220 snoRNAs, 8 small cytoplasmic RNAs and 10 ribosomal RNAs. In an initial exploratory data analysis, we conducted a principal component analysis of all signals detected to assess the potential value of the data sets to segregate mTBI and non-mTBI cases. The analysis revealed that data sets from all cases can be clustered into an mTBI or non-mTBI group, with the exception of mTBI case #33811, which is plotted far from the mTBI and non-mTBI clusters (Figure 1). Results from the principal component analysis suggested that the dataset generated from case #33811 was an outlier. Based on this and the fact that the quality of RNA extracted from this case was poor (not shown), we excluded case #33811 from subsequent statistical analyses.
Biological surrogates for distinguishing TBI from PTSD

Using high throughput small non-coding RNA datasets, we continued to search for candidate mTBI biomarkers that are differentially regulated in PBMCs of mTBI compared to non-mTBI cases. Two criteria were used to identify candidate small RNA biomarkers for mTBI: 1) group changes (mTBI vs. non-mTBI groups) must be associated with a magnitude of ≥1.5-fold, and 2) group changes must be statistically significant with p < 0.05, based on t-test analysis followed by the application false discovery rate corrections for multi-sampling errors. We identified 18 candidate small RNA biomarkers meeting both criteria: 4 miRNAs, 13 snoRNAs and 1 small scaRNA. Interestingly, we observed that all candidate small RNA biomarkers are significantly down-regulated in mTBI versus non-mTBI cases. In an unsupervised clustering analysis using RNA expression data generated from the high-throughput gene chip platform for the 18 candidate small RNA biomarkers, we were able to correctly segregate all 17 mTBI and non-mTBI cases analyzed (Figure 2), implicating their potential value as surrogate biological indices for mTBI among the OEF/OIF Veteran population.

Independent qPCR validation of candidate small non-coding RNA biomarkers

We next used an independent quantitative real-
Biological surrogates for distinguishing TBI from PTSD

time polymerase chain reaction (qPCR) procedure to assess the expression of individual candidate small RNA biomarkers in PBMC specimens from the same 9 mTBI and 9 non-mTBI cases used in our high-throughput biomarker discovery studies. Primer sets specific for each of the biomarkers were custom-designed and synthesized commercially by Applied Biosystems (Carlsbad, CA). Using these primer sets, we conducted qPCR studies and assessed the contents of individual candidate small RNA biomarkers in PBMCs of mTBI compared to non-mTBI cases. Results from our qPCR studies confirmed that 13 of the 18 candidate small RNA biomarkers are, indeed, differentially regulated in PBMCs of mTBI compared to non-mTBI veteran cases (Figure 3). The 13 confirmed small RNA biomarkers include 12 small nucleolar RNA (ACA48, ENSG199411, HBlI-239, HBII-289, U15B, U27, U35A, U55, U56, U58B, U83A, U91) and 1 miRNA (Has-miR-671-5p) (Figure 3). Consistent with evidence from our RNA array platform, each of the 13 confirmed small RNA biomarkers are found in significantly lower levels in PBMC specimens from mTBI compared to non-mTBI veteran cases (Figure 3).

Exploring the potential value of novel small RNA biomarkers for segregating mTBI from non-mTBI veteran cases

Based on results from our qPCR biomarker confirmation studies, we next assessed the value of the 13 confirmed small RNA biomarkers as a criterion to correctly diagnose mTBI versus non-mTBI veteran cases. Using an unsupervised clustering analysis, we found the 13 confirmed mTBI biomarkers effectively segregated the cases correctly into mTBI and non-mTBI groups, with the exception of 2 of the non-mTBI cases which were incorrectly identified as mTBI (Figure 4A). We continued unsupervised clustering analyses to test the efficacy of individual or a combination of qPCR confirmed biomarkers to correctly segregate mTBI and non-mTBI veteran cases. Outcomes from these analyses led to the identification of a 3 small nucleolar biomarker panel, comprised of HBII-289, ENSG199411 and U35A, which is capable of distinguishing mTBI from non-mTBI veteran cases with 89% accuracy, 82% selectivity and 78% specificity (Figure 4B).

Discussion

Evidence has suggested that appropriate interventions can reduce functional impairment after mTBI [30,31,32,33]. In order to demonstrate the efficacy of clinical interventions, research must identify the biological, clinical, and neurological indices that are sensitive to the detection of functional impairments after mTBI. Results from our studies led to the identification of 13 novel clinically accessible small RNA mTBI
biomarkers, including 12 small snoRNA and 1 miRNA. Using qPCR, we have independently confirmed that each of these biomarkers is significantly down-regulated in PBMC specimens from mTBI compared to non-mTBI veteran cases. Among the 13 mTBI biomarkers, we demonstrated that a panel of 3 snoRNA - HBII-289, ENSG199411 and U35A - is capable of distinguishing mTBI from non-mTBI veterans with 89% accuracy, 82% selectivity and 78% specificity. Collectively, our evidence suggests that additional applications of the small RNA biomarkers we have identified, particularly the three biomarker panel, to current diagnostic criteria may improve mTBI detection and provide more sensitive outcome measures for clinical trials.

PTSD is commonly co-morbid with mTBI in OEF/OIF Veterans [34,35]. We note that the majority of Veterans with mTBI in our biomarker study have co-morbid PTSD and that our non-mTBI
Biological surrogates for distinguishing TBI from PTSD

Cases are selected to match for PTSD diagnosis. Thus, our identified 13 small RNA biomarkers likely represent biological indices selective for mTBI. Moreover, mTBI cases in our biomarker discovery studies were recruited after an average interval of 3.9 years following their last deployment (deployment-to-recruitment interval: ranging from 0.7 to 10.2 years, with a median interval of 3.4 years) (Table 1). Thus, changes in the regulation of these small RNA mTBI biomarkers that we observed are not acute mTBI responses, but likely represent long-term physiological consequences subsequent to mTBI experienced during deployment.

The pathological implication of our observation that select small nucleolar RNA and miRNA are differentially regulated in the PBMCs of mTBI relative to non-mTBI veteran cases is currently unknown. Small nucleolar RNA and miRNA are members of a family of non-coding RNAs that are involved in many physiological cellular processes and are also known to contribute to molecular alterations in pathological conditions [36]. SnoRNAs are short RNA sequences comprised of ~60-220 nucleotides. They are primarily known for their role as guide molecules for site-specific methylation and pseudouridylation of other RNAs, particularly rRNA, as well as tRNA and small nuclear RNAs. These chemical alterations are required for proper RNA processing and ribosome function as well as for proper function of the spliceosome [37]. MicroRNA are short (~22 nucleotides) RNA sequences that bind to complementary sequences on target mRNA, thereby blocking translation or promoting degradation of target mRNA [37]. SnoRNA and miRNA are expressed in the brain and both classes of small RNAs have been implicated in neuroplasticity mechanisms and neurological disorders. For example, recent evidence suggests a role of the HBII52 small nucleolar RNA in the regulation of alternative splicing of the serotonin 2c receptor [38], and that patients with autism and Prader-Willi-like characteristics are found to have reduced levels of HBII52 in the brain [39]. The miRNA miR132 is induced by neuronal activity and neurotrophins in a CREB-dependent manner and plays a role in regulating neuronal morphology and cellular excitability [40]. Moreover, preclinical evidence in rodent models demonstrated that small RNA expression is affected in the brain by TBI. Redell et al. [8] reported transient elevated expression

Figure 3. Independent quantitative real-time polymerase chain reaction (qPCR) assays confirmed that 13 small RNA TBI biomarkers are differentially regulated in PBMCs of mTBI relative to non-mTBI control cases. PBMC contents for each of the 18 candidate small RNA biomarkers identified by the high-throughput Array Chip platform in Figure 2 were quantitatively assessed using independent qPCR assays. The same 9 mTBI and 9 non-mTBI cases (Table 1) we used in our initial high-throughput biomarker discovery assay were assessed in this qPCR biomarker confirmation study. Bar graphs represent mean small RNA biomarker contents in the mTBI group relative to the non-mTBI group; error bars represent standard errors. * False discovery rate-corrected P-value < 0.05. qPCR confirmed 13 small RNA biomarker species are significantly down-regulated in PBMC of mTBI compared to non-mTBI veteran cases. These 13 confirmed small RNA biomarkers include 12 small nucleolar RNA (ACA48, ENSG199411, HBII-239, HBII-289, U58B, U58, U56, U58E, U58B, U58F, U6, U7, U35A, U35A, U35B, U35A, U35B) and 1 miRNA (Has-miR-671-5p) species.
Biological surrogates for distinguishing TBI from PTSD

of the miRNA miRNA-21 in rats following an impact injury to the brain. Using a high-throughput Array Chip platform, Lei et al. [41] reported potential aberrant up- or down-expression of 203 miRNA species in the rat cerebral cortex up to 72 hrs following fluid percussion injury to the brain. Redell et al [42] also identified potential up-regulation of 35 and down-regulation of 50 miRNA species in the hippocampus of rats within 72 hrs following an impact TBI to the brain; altered regulations for a smaller subset of 8 (4 up-regulated and 4 down-regulated) miRNA species in the hippocampus were subsequently confirmed by independent qPCR.

It is possible that the altered regulation of select small nucleolar RNA and miRNA that we observed in PBMCs of veteran mTBI cases might have implications in the central nervous system. Genes relevant to neural circuits, synapses and neural plasticity processes are also expressed in circulating blood cells, such as PBMCs. Thus, the fact that we observed significant down-regulation of select small RNA biomarkers in PBMC specimens from our veteran mTBI cases long after their deployment might reflect long-term molecular alterations in the central nervous system contributing to the onset and progression of clinical TBI phenotypes. Future studies exploring the physiological relevance of mTBI biomarkers will provide a better understanding of the biological mechanisms underlying mTBI and insights into novel therapeutic targets for mTBI.

**Acknowledgments**

These studies are supported by a Department of Defense award (W81XWH-08-2-0026) to Giulio Maria Pasinetti and in part by the National Institutes of Health (grant AG029310).

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Biological surrogates for distinguishing TBI from PTSD


