Neurobehavioral and Psychological Health Outcomes

A Pilot Study to Understand the Differentiating Factors for Traumatic Brain Injury (TBI) from Posttraumatic Stress Disorder (PTSD) Patients

TBI has become the “signature wound” of Operation Iraqi Freedom (OIF)/Operation Enduring Freedom (OEF). Due to the increasing use of improvised explosive devices (IEDs) by the insurgency and the necessary facial exposure of our combat troops even when wearing protective gear, estimates suggest that as many as 20 to 30 percent of returning Service Members may eventually exhibit symptoms of TBI. PTSD as defined by the American Psychiatric Association is a serious behavioral health disorder, and it has been estimated that 17.1 percent of Service Members returning from Iraq and 11.2 percent of those returning from Afghanistan have experienced major depression, generalized anxiety, and/or PTSD. As a part of the present effort investigators at the Integrative Systems Biology Program (US Army Centner for Environmental Health Research (USACEHR)) are working with collaborators from Dwight D. Eisenhower Army Medical Center screening for potential biomarkers associated with neuronal injury. In this pilot study, blood samples were collected and shared with USACEHR for multi-omics analysis for identification of candidate genes/proteins. The candidate gene/protein approach is viewed as only a first step toward identifying molecular mechanisms likely to be involved in the physiologic consequences of TBI/PTSD. Gene expression, DNA methylation, and targeted proteomics analysis have been completed in these samples (Figure 1), and functional pathway predictions show possible overlaps between networks enriched by differentially expressed genes and methylated genes (Figure 2). The advancement of the current findings from the USACEHR group needs to be validated using a larger sample size, and it will be important to include a gender/age/ethnicity matched control population. The results of this research will be leveraged in multiple ways to improve the health and treatment of returning Service Members diagnosed with TBI and with PTSD.

FIGURE 1: Pathways Differentially Expressed in Blood Samples from TBI/PTSD Compared to TBI

Ingenuity Canonical Pathways	Upregulation	Downregulation
PI3K/AKT Signaling	11	6
mTOR Signaling	8	6
Protein Ubiquitination Pathway	5	7
Neuregulin Signaling	10	6
Telomere Extension by Telomerase	20	13
PEDF Signaling	13	3
AMPK Signaling	4	7
TGF-beta Signaling	11	2
Cyclins and Cell Cycle Regulation	6	8
VEGF Signaling	10	3
Gap Junction Signaling	7	4
EIF2 Signaling	5	5
p53 Signaling	8	4
CDK5 Signaling	6	6
Telomerase Signaling	5	7
Cell Cycle Regulation by BTG Family Proteins	9	9
NRF2-mediated Oxidative Stress Response	6	4
ErbB2-ErbB3 Signaling	11	4
Ceramide Signaling	8	5
Wnt/beta-catenin Signaling	7	4
PTEN Signaling	9	2
Epithelial Adherens Junction Signaling	7	3
Dopamine-DARPP32 Feedback in cAMP Signaling	5	5
RAR Activation	7	2
Nitric Oxide Signaling in the Cardiovascular System	6	5
Apoptosis Signaling	8	3
Synaptic Long Term Depression	5	5
ILK Signaling	6	3
Axonal Guidance Signaling	4	4
Insulin Receptor Signaling	6	4
Huntington's Disease Signaling	5	3
ERK/MAPK Signaling	5	4
Synaptic Long Term Potentiation	6	4
PPAR Signaling	6	4
NGF Signaling	7	3
Glutamate Receptor Signaling	7	5
Glucocorticoid Receptor Signaling	5	3

FIGURE 2: Brain Derived Neurotrophic Factor (BDNF) Network Differentially Expressed in Blood Samples from TBI/PTSD Compared to TBI