Pathophysiology of Neurotrauma

Identifying a Candidate Panel to Discriminate Traumatic Brain Injury from Posttraumatic Stress Disorder-Traumatic Brain Injury Polytrauma Symptoms

Traumatic brain injury (TBI) is the "signature wound" of Operation Iraqi Freedom (OIF)/Operation Enduring Freedom (OEF). Due to the increasing use of improvised explosive devices by the insurgency and the necessary facial exposure of combat troops even when wearing protective gear, it is estimated that 20 to 30 percent of returning Service members may eventually exhibit symptoms of TBI (*Scholten et al. 2012*). Posttraumatic stress disorder (PTSD) is a serious behavioral health disorder, and it has been estimated that 17.1 percent of soldiers returning from Iraq and 11.2 percent of those returning from Afghanistan have experienced major depression, generalized anxiety, and/or PTSD (*Richardson, Frueh, and Acierno 2010, Xue et al. 2015*). As part of the present effort, researchers at the Integrative Systems Biology Program at U.S. Army Center for Environmental Health Research (USACEHR; Frederick, Maryland) are working with collaborators from the Dwight D. Eisenhower Army Medical Center (DDEAMC; Augusta, Georgia) to screen for potential biomarkers associated with neuronal injury. In a pilot study, researchers at DDEAMC collected blood samples from individuals with PTSD or with mild traumatic brain injury (mTBI) and PTSD, and shared these samples with USACEHR for multi-omics analysis. The goal was to identify candidate genes/proteins differentially expressed between those who were diagnosed as having PTSD from those diagnosed with mTBI and PTSD. The candidate gene/protein approach is viewed as only a first step toward identifying molecular mechanisms that are likely to be involved in the physiologic consequences of mTBI and PTSD. Gene expression, deoxyribonucleic acid (DNA) methylation, and targeted proteomic analyses have been completed for these samples, and functional pathway predictions show possible overlaps between networks enriched by differentially expressed and methylated genes (Figure 1).

> Correlation of clinical data with omics results will help identifying a candidate panel to discriminate TBI from PTSD-TBI polytrauma symptoms.

The clinical, anthropometric, physical, biometric, and endocrine data collected by DDEAMC will be sent to USACEHR researchers, who will correlate these data with the omics results to identify a candidate panel to discriminate TBI from PTSD-TBI polytrauma symptoms.

USACEHR researchers are engaged in validating the epigenetic markers using a low throughput targeted platform. Based on published studies of PTSD patients among OIF/OEF Veterans, it is anticipated that the DNA methylation pattern has the potential to serve as an early detection marker, but this requires further validation (*Hammamieh et al. 2017*). The USACEHR researchers are in the process of validating the regions that were identified using Human450K methylation data and will interrogate CpG sites within these regions of interest by pyrosequencing of amplicons in real-time.

This research was funded by intramural funding strategically aligned with Military Operational Medicine Research Program and Combat Casualty Care Research Program.

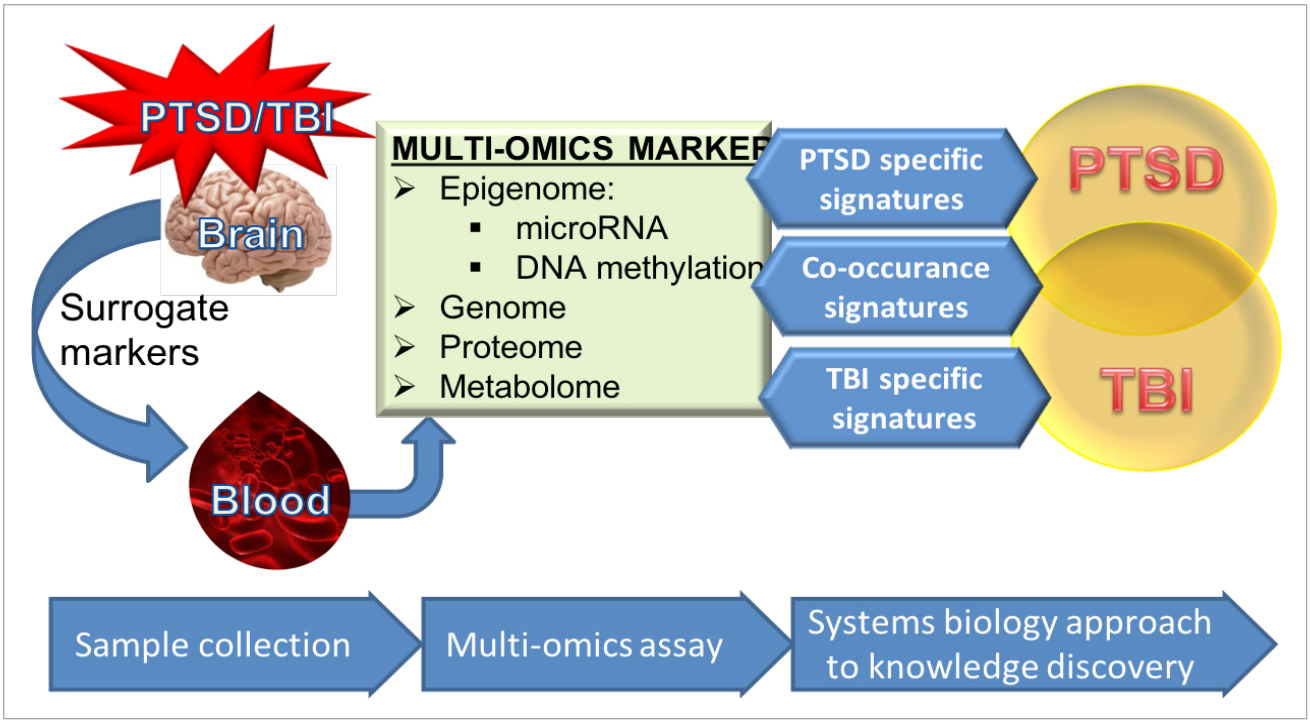

FIGURE 1: The systems biology approach to derive biologically meaningful information towards the precision disease diagnostics for PTSD and TBI, two signature diseases of OEF/OIF warfighters and veterans (Figure used with permission from the authors)

REFERENCES:

Hammamieh, R., Chakraborty, N., Gautam, A., Muhie, S., Yang, R., Donohue, D., Kumar, R., Daigle, B. J., Jr., Zhang, Y., Amara, D. A., Miller, S. A., Srinivasan, S., Flory, J., Yehuda, R., Petzold, L., Wolkowitz, O. M., Mellon, S. H., Hood, L., Doyle, F. J., 3rd, Marmar, C., and Jett, M. 2017. "Whole-Genome DNA Methylation Status Associated with Clinical PTSD Measures of OIF/OEF Veterans." Transl Psychiatry 7 (7):e1169. doi: 10.1038/tp.2017.129.

Richardson, L. K., Frueh, B. C., and Acierno, R. 2010. "Prevalence Estimates of Combat-Related Post-Traumatic Stress Disorder: Critical Review." Aust N Z J Psychiatry 44 (1):4-19. doi: 10.3109/00048670903393597.

Scholten, J. D., Sayer, N. A., Vanderploeg, R. D., Bidelspach, D. E., and Cifu, D. X. 2012. "Analysis of US Veterans Health Administration Comprehensive Evaluations for Traumatic Brain Injury in Operation Enduring Freedom and Operation Iraqi Freedom Veterans." Brain Inj 26 (10):1177-84. doi: 10.3109/02699052.2012.661914.

Xue, C., Ge, Y., Tang, B., Liu, Y., Kang, P., Wang, M., and Zhang, L. 2015. "A Meta-Analysis of Risk Factors for Combat-Related PTSD among Military Personnel and Veterans." PLoS One 10 (3):e0120270. doi: 10.1371/journal.pone.0120270.