Treatment Strategies

Assessment of Cytokine Levels in Plasma, Brain, and Retina of a Rat Model of Blast-induced Mild Traumatic Brain Injury (mTBI), Using Immunoassay Arrays

Chemokines and cytokines play early pivotal roles in the inflammatory cascades underlying blast-induced injuries and are promising targets for therapeutic interventions. To effectively pursue this therapeutic avenue, the timing of the interplay among these responses must be characterized to identify the key participants and the optimal therapeutic windows for intervention. Cytokine levels in plasma, brain, and retina are being longitudinally screened at varied times after blast exposure using immunoassay arrays based on newly developed Luminex® bead technology. The arrays (R&D Systems Inc.) are used to precisely simultaneously quantify very small concentrations (pico-molar) of up to 17 rat specific cytokines across a single 96 sample well plate. Thus, this method is highly time and cost effective. Analyses to date of plasma and brains collected from blast-exposed rats reveal marked increases (> 2-fold) in the pro-inflammatory cytokines Chemokine (C-X-C motif) ligand 2 (CXCL2), CXCL3, intercellular adhesion molecule 1, interleukin 1 alpha (IL-1α), IL-6, and tumor necrosis factor alpha along with elevations in the inflammation resolving cytokines IL-4 and tissue inhibitors of metalloproteinase 1 up to seven days post-insult. We have also shown using magnetic resonance imaging (MRI) (fluorine-19 (19F)-MRI) of an intravenously injected perfluorocarbon contrast agent which is readily taken up by macrophages that extensive immune cell infiltration occurs within the brain and retina by three days post-exposure. These findings have been corroborated by immunohistochemistry of brain and eye sections using biomarkers for activated immune cells, (e.g., Iba1 and cluster of differentiation 68 (CD68)). Cytokines can act as recruitment factors for macrophages into tissues, and in turn are excreted by these immune cells as signaling molecules that further trigger protein-pathways involved in apoptosis of neurons, (e.g., caspases). Based upon these response profiles, interventions with existing compounds targeting these mediators are likely to be most effective during subacute or acute phases of injury. By revealing the neurobiological mechanisms that underlie blast overpressure (BOP)-induced TBI, these experiments will provide valuable insights into mitigation strategies and therapeutic countermeasures for affected Service Members.