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Psychological Stress and Prolonged Anxiety: Key Neuroimmune interactions between Microglia, Monocytes, and Endothelia

Dr. Godbout is a Professor of Neuroscience at the Ohio State University Wexner Medical Center. He is the Faculty Director of the Chronic Brain Injury Program, the Co-Director of a NINDS T32 Training grant (Neuroimmunology) and a member of the Institute for Behavioral Medicine Research. Dr. Godbout has a B.S. (1996) and a Ph.D. (2001) from the University of Illinois-Urbana and was a NRSA supported post-doctoral fellow with Dr. Rodney Johnson. Dr. Godbout's background is in neuroscience, immunology, and behavior with specific expertise in aging, neuroimmunology (e.g., microglia, astrocytes, and cytokines) and affective behavior (anxiety, sickness, depression). As a Principal Investigator, Dr. Godbout aims to determine the degree to which the bi-directional communication between the immune system and brain is affected by aging, psychological stress, and traumatic brain injury. In addition, he aims to delineate the mechanism by which inflammatory cytokine signaling causes long-lasting complications (e.g., anxiety, cognitive decline and depression). Dr. Godbout is an author on over 100 publications and his research is/has been supported by grants from the NIH (NIA, NINDS & NIMH), AFAR, DOD, Abbott Nutrition, and OSUMC. The Godbout laboratory has been productive and published several relevant and impactful "Neuroimmunology" and "Neurotrauma" papers, including reports in Journal of Neurotrauma, Brain, Behavior, and Immunity, Journal of Neuroscience, Glia, Biological Psychiatry, Molecular Psychiatry and Immunity. Dr. Godbout is active in the scientific community with membership in the Society for Neuroscience, National Neurotrauma Society and PsychoNeuroImmnology research Society (PNIRS). He serves on the Editorial Boards for the Journal of Neuroinflammation and Brain Behavior and Immunity. In addition, Dr. Godbout is a standing member of the BNRS NIH study section and serves on the President's council for PNIRS. Last, Dr. Godbout has received several awards including the PNIRS New Investigator Award (2009), the Siddens Award for Distinguished Faculty Advising (2012), the Neuroscience Faculty Research Award (2013 & 2017) and OSU Excellence in Research Award (2018).

Abstract: Psychological stress contributes to the development of anxiety and depression. Recent clinical studies have reported increased inflammatory leukocytes in circulation of individuals with stress-related psychiatric disorders. Parallel to this, our work with repeated social defeat (RSD) in mice shows that this stressor causes release of inflammatory monocytes into circulation. In addition, RSD caused the

development of prolonged anxiety that was dependent on microglia activation and the accumulation of inflammatory monocytes within the brain vasculature. Therefore, we hypothesize that chronic stress drives unique immune to brain signaling events that augment neuroinflammatory signaling and prolong anxiety. We provide evidence of threat appraisal activation that spatially coincided with microglial activation and endothelial facilitation of monocyte recruitment. Moreover, microglial depletion with a CSF1R antagonist prior to stress prevented the recruitment of monocytes to the brain and abrogated anxiety. Transcriptional profiling revealed unique mRNA signatures of monocytes in the blood, monocytes in the brain and microglia in the brain after RSD. For example, microglia selectively enhanced the expression of key chemokines, while monocytes highly expressed IL-1β, MMP9 and Ly6C. Moreover, the monocyte inflammatory profile was also dependent on IL-6. Consistent with these profiles, the recruited inflammatory monocytes with stress adhered and activated IL-1R1+ neurovascular endothelia through an IL-1β (caspase-1 dependent) signaling mechanism. Cell specific RiboTag capture revealed an endothelial mRNA profile that was enriched in cyclooxygenase (COX) and prostaglandin signaling pathways after this IL-1β mediated activation with stress. Intervention with the COX-2 inhibitor, Celecoxib (CCB), reduced PGE2 production and blocked anxiety-like behavior in response to RSD. Collectively, prolonged anxiety following RSD was caused by microglial recruitment of IL-1β-producing monocytes that activated brain endothelia.