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Editorial

Taming the storm

Tal Burstyn-Cohen[a,*] and Ning Quan[b,*]
[a]*Institute for Oral and Biomedical Research (IBOR), Faculty of Dental Medicine, The Hebrew University, Jerusalem, Israel*
[b]*Department of Biomedical Science, Charles E. Schmidt College of Medicine, Stiles-Nicholson Brain Institute, Florida Atlantic University, Jupiter, FL, USA*

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Research in the last 5 decades has consolidated our understanding of the critical roles of neuroimmune communication in the maintenance of homeostasis and in the pathogenesis of peripheral and central nervous system related diseases. This is especially relevant to today's world of COVID-19, in which many suffer from the consequences of the "cytokine storm" induced by the infection of the Sars-Covid-2. In vital peripheral organs, hyper-expression of proinflammatory cytokines after viral infection often results in significant immune mediated damage, sometimes leading to death, turning body's defense mechanism into a cause of its demise. The survivors of COVID-19 also show long-haul mental health disorders, likely caused by the long-lasting secondary cytokine storm that ensues in the central nervous system. In this special issue of Brain Plasticity, Muscat and Barrientos reviewed accumulated evidence that explains how immune activation initiated in the periphery might sensitize microglial cells of the brain to translate peripheral cytokine storm into a central menace, especially in the elderly. They described multiple pathways by which peripheral immune activation stimulates neuroinflammation in the brain, characterized the changes in microglial cells through their transformation into the sensitized and potentially harmful phenotype, discussed downstream mechanisms by which inflammatory microglia cause deficits in cognitive function, reduce neural synaptic plasticity, and impair memory. What is uniquely salient about this review is its synthesis of the "multi-hit" theory. Behind the usually protective blood brain barrier, microglial senescence, high-fat diet, surgical trauma, oxidative stress, psychological stress, and compromised blood brain barrier primes the vulnerability of the central nervous system, allowing a significant peripheral infectious event, such as COVID-19, to tip the system into a prolonged state of dysfunction. They point out that a crucial cytokine in this brain cytokine storm is interleukin-1 (IL-1).

In the second paper of this issue, Nemeth and Quan provided an update on the current understanding of how IL-1 modulates neural networks. Recent studies revealed that the receptor for IL-1, IL-1R1, is expressed in the brain by multiple cell types and by specific sets of neurons, contrary to previous assumption that all cells of the brain might express varying levels of IL-1R1. In addition, genetic tools are now available to track and manipulate IL-1R1 expression in specific cell types and in specific brain regions. Distinct neuroimmune effects mediated by IL-1 can now be analyzed on the cell type specific basis, heralding in new paradigms to explain how this pivotal cytokine might regulate neural network activity. They posited

*Correspondence to: Tal Burstyn-Cohen, PhD., Faculty of Dental Medicine, The Hebrew University, Ein-Kerem Medical Campus, Jerusalem 9112102, Israel. Tel. (Office): +972 2 675 8582; E-mail: talbu@mail.huji.ac.il. and Ning Quan, PhD., Biomedical Science, Charles E. Schmidt College of Medicine, Stiles-Nicholson Brain Institute, Florida Atlantic University, Room 228, MC-17, 5353 Parkside Dr., Jupiter, FL 33458, USA. Tel.: +1 614 316 2925; E-mail: nquan@health.fau.edu.

in this review that very low concentrations of IL-1 are involved in the normal neural functions of the brain through its interaction with the high-sensitivity IL-1R1 expressed by specific sets of neurons and astrocytes, whereas inflammatory activities of the IL-1 are mediated by IL-1R1 expressed by endothelial cells and ventricular cells in the brain. Further, because IL-1R1 is now known to be expressed only in certain neurons, its modulation on a presynaptic neuron could be different from that on a postsynaptic neuron. In addition, IL-1R1 is not expressed by the neural stem cells in the brain, suggesting that the previously reported anti-neurogenic effects of IL-1 are mediated indirectly via IL-1R1 expressed on non-neuronal cell. Thus, translating cytokine storm into neural dysregulation may depend on these novel mechanisms.

Taming the cytokine storm is a task performed by TAMs. In the third paper of this issue, Hochberg and Burstyn-Cohen review the multifarious roles this signaling pathway takes when the CNS experiences a cytokine storm, and also under the calmness of healthy homeostasis. The roles fulfilled by Tyro3, Axl and MerTK (hence TAM) receptors and their ligands Protein S (PROS1) and Growth-arrest-specific 6 (GAS6) span a wide range of cell types and vary dramatically. Expressed by microglia – the immune cells of the CNS- TAMs perform bona fide immune-related roles as regulation of inflammation and cytokine secretion both in health and in disease. An overview of the recent studies examining the roles of TAM signaling molecules in disease includes models of Alzheimer's and Parkinson's Disease, Ischemia and Multiple Sclerosis. Since TAMs are expressed by nearly every cell type in the CNS, the intricate TAM-based interactions between microglia, astrocytes, neurons, endothelial cells, oligodendrocytes, stem and mature cells provide opportunities for abundant intercellular interactions. In the fit brain, TAM signaling contributes to homeostasis through regulating both adult neurogenesis and synaptic signaling through performing maintenance and cleaning operations which include debridement and pruning of synapses by both microglia and astrocytes. A comprehensive description is dedicated to cover how TAMs and their ligands shape adult neurogenesis - a vitally important process for brain plasticity - through regulating neural stem cell (NSC) biology and influencing NSC physiology. The NSC - adult neurogenesis platform reveals different roles for different TAM signaling members and suggests how this family of signaling molecules can fine-tune adult neurogenesis through interaction with the Notch and Bmi-1 pathways. Thus, in the CNS TAMs not only function as an independent signaling axis, but also have a broader impact thought modifying additional key pathways.

A closer look into the transcriptional regulation of the TAM receptor MERTK is provided by Walsh and colleagues. MERTK expression is enriched in the CNS and in resident innate immune cells where it regulates numerous functions that support brain plasticity, and polymorphisms in the MERTK gene are associated with Multiple Sclerosis. This study provides a detailed analysis of the 5Kb region upstream of the MERTK transcription start site, and finds binding sites for general and tissue specific transcription factors. Interestingly, glucocorticoid binding elements were not identified in this region, indicting that other transcriptional regulatory cis-acting domains promote MERTK responsiveness to glucocorticoids. Incorporating these data may advance strategies to therapeutically intervene and regulate MERTK transcription in various diseased states, to tailor inflammatory signaling and efferocytosis which may affect multiple aspects of brain plasticity.

Overall, as reflected by this issue and by additional works elsewhere, neuroimmune interactions are emerging as key regulators of brain plasticity throughout life and in health and disease.