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From stress sensitization to microglial priming and vice versa: a new era of research in biological psychiatry

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The world of stress-related research used to be quite straightforward. Based on animal models of stress it was commonly accepted that anxiety- and depression-like behavior induced by acute or repeated exposure to inescapable stressors could be explained by the interaction between peripherally released stress mediators, represented mainly by glucocorticoids and catecholamines, and brain neurotransmitters. We also knew that stressors can affect immune responses at the periphery not only because of the sensitivity of immune cells to stress hormones but also because of the innervation of the lymphoid organs by the sympathetic nervous system. However, there was no reason to believe that the peripheral immune response was of much importance for stress-induced anxiety and depression as the brain was supposed to be protected from what is going at the periphery by the blood-brain barrier.

This simplistic view had to be abandoned in the 1980s when it became apparent that peripheral innate immune responses impact brain functions because of their ability to engage the same immune cell types and communication molecules in the brain as those that mediate the inflammatory response at the periphery [1]. This allowed the emergence of the concept of bidirectional communication between the brain and the immune system, allowing the organism to quickly mobilize its immune cells when it runs into the risk of being injured during exposure to stress and facilitating recovery once the stress episode is over by promoting care of the injured body.

Microglia play a key role in this process. They become activated in response to the immune signals they receive from the periphery and they release immune mediators that organize the host response to infectious agents, the so-called pathogen molecular patterns, or to molecules released by damaged cells, the so-called damage-associated molecular signals. Importantly enough, there is no need for the blood-brain barrier to be disrupted in this process as multiple communication pathways between the immune system and the brain circumvent this barrier, including the sensory nerves that innervate the injury site and the brain endothelia that sense circulating pathogen-associated molecular patterns or danger signals and relay this information to microglia via perivascular macrophages. The term neuroinflammation refers to the sterile inflammation that develops in the brain in response to

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the peripheral inflammatory response. It is mediated by the production of proinflammatory cytokines by brain resident macrophages and microglia.

The surge in research on neuroimmune interactions during the last two decades has opened a new era in biological psychiatry built on the hope that the “neuroimmune window” to the brain will be more successful than the “neuroendocrine window” has been. The objective is much more ambitious as it aims to decipher the contribution of neuroimmune processes to the pathophysiology of psychiatric disorders and to develop personalized targeted therapies on the basis of this knowledge. The booming research in this field is at the origin of a new branch of psychiatry called immunopsychiatry [2] which is to psychiatric disorders what immunodermatology is to immune-mediated skin diseases.

To come back to stress, the work of John Sheridan and his colleagues at the Ohio State University Health Sciences Center in Columbus recapitulates in an exemplar manner this paradigmatic shift from stress to immunopsychiatry. While working on the effects of social stress on immune cells in mice in the 2000s, Sheridan observed that social defeat induces corticosterone resistance in splenocytes [3]. This turned out to be due to the trafficking of myeloid progenitor cells into the spleen. Compared to resident splenocytes, myeloid progenitors were known to be not only resistant to glucocorticoids but also more inflammatory. As social defeat caused reliable anxiety-like alterations in behavior[4], it was tempting to determine whether the increased inflammatory phenotype of socially defeated mice played any role in the development of their anxiety-like behavior. The recruitment of Jonathan Godbout in 2005 at the newly founded Institute for Behavioral Medicine Research at OSU provided the missing link. Having been trained in the role of immune-to-brain communication pathways in the development of inflammation-induced sickness and depression at the University of Illinois at Urbana-Champaign, it did not take long to the research team formed by Godbout and Sheridan to investigate whether microglia are activated in the brain of socially defeated mice [5]. Not only was microglia found to be activated but this activation which was key to the development of anxiety-like behavior was demonstrated to be dependent on the trafficking of monocytes to the brain of socially defeated mice. This meant that neuroinflammation in socially defeated mice was not only a molecular process mediated by the production of proinflammatory cytokines in the brain but also a cellular process dependent on the recruitment of peripheral immune cells to the brain vasculature. The next question was obviously to determine whether the brain trafficking of inflammatory monocytes was sufficient to explain the neuroinflammatory response or it required some form of cooperation between trafficking and resident innate immune cells in the brain. This was a tricky question. There is no easy way to eliminate resident innate immune cells in the brain without running into the risk of altering at the same time peripheral innate immune cells. In addition, irradiating the head to deplete microglia results into leaky blood-brain barrier, which facilitates trafficking of cells and molecules having nothing to do normally in the brain. Godbout opted instead for using an inhibitor of the receptor for colony stimulating factor 1 (CSF1R).

CSF1 is a lineage-specific hematopoietin that stimulates proliferation and supports differentiation and survival of cells of the mononuclear phagocyte series [6]. As CSF1R is overexpressed on tumor-associated macrophages that play a pivotal role in tumor growth and

immunotolerance, a number of biotechnology companies have embarked on the identification and characterization of CSF1/CSF1R targeting agents, with some of them in clinical development. Emerging roles for the CSF1R and its ligands in the nervous system have also become apparent, making these compounds of potential interest in neuropathology [7]. All of this has made available CSF1R antagonists that can be used as research tools to selectively deplete peripheral macrophages or microglia and peripheral macrophages depending on their brain penetrance. This did not escape Godbout's attention as he was looking for a way to deplete microglia without altering monocytes (or myeloid cells) and their ability to traffic from the bone marrow to other organs including the brain. In a first series of experiments with a brain penetrant CSF1R antagonist, PLX5622, he elegantly demonstrated that elimination of microglia abrogates recruitment of myeloid progenitor cells into the brain and blocks the development of anxiety[8]. In a second series of experiments of which the results are published in this issue of Biological Psychiatry, he used the same tool to investigate the relative importance of microglial and neuronal sensitization in the phenomenon of stress sensitization [9]. Stress sensitization typically occurs when individuals exposed to a subthreshold stressor are acutely re-exposed days or weeks later to the same or a qualitatively different stressor and show a marked response to it despite this secondary stimulus having no effect on its own. The findings reported by Godbout, Sheridan and their team in this issue of Biological Psychiatry are important because they show for the first time that neuroinflammation contributes to the development of stress sensitization. Mice treated with the CSF1R antagonist to eliminate their sensitized microglia before being exposed to the acute social defeat did not display any monocyte recruitment to the brain nor any sign of anxiety after social defeat. When microglia were allowed to self-renew following elimination, the microglia population that took over showed no evidence of sensitization but stress sensitization was maintained. These findings were interpreted to suggest that stress sensitization involves both neuronal and microglial-dependent processes.

Immunologists have long known that macrophages can be sensitized or in the immunological language "primed" i.e., made more reactive to subsequent re-stimulation. Like macrophages, microglia are exposed to a wide variety of metabolic, homeostatic and immune-regulatory signals in their microenvironment, which influence their basal functions and responses to danger signals. These signals activate a network of transcription factors of which the ability to elicit changes in gene expression depends on the accessibility of their DNA binding sites. At the molecular level, priming involves the binding of stimulus-regulated transcription factors either at pre-existing enhancer like regions of the genome or at closed regions of the genome, leading to the acquisition of histone modifications associated with enhancers [10]. As the exact nature of enhancer landscapes is shaped by the tissue environment, it is obvious that studies like the ones carried out by Godbout, Sheridan and their colleagues, based on very well controlled psychosocial factors will help ultimately to decipher the cellular and molecular mechanisms of the dysregulation of neuroimmune interactions involved in the development and recurrence of psychiatric disorders like anxiety and depression.

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