From Stress Sensitization to Microglial Priming and Vice Versa: A New Era of Research in Biological Psychiatry

Robert Dantzer

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 could 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 because 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 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 because 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 that relay this information to microglia via perivascular macrophages. The term “neuroinflammation” refers to the sterile inflammation that develops in the brain in response to 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 2 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 based on 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.

The work of John Sheridan and his colleagues at the Ohio State University Health Sciences Center in Columbus recapitulates in an exemplary manner this paradigmatic shift from stress to immunopsychiatry. While working on the effects of social stress on immune cells in mice in the 2000s, Avitsur *et al.* (3) observed that social defeat induces corticosterone resistance in splenocytes. This turned out to be caused by the trafficking of myeloid progenitor cells into the spleen. Compared with resident splenocytes, myeloid progenitors were known to be not only resistant to glucocorticoids but also more inflammatory. Social defeat caused reliable anxiety-like alterations in behavior (4), and 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 Ohio State University provided the missing link. Godbout was 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, and 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 [Wohleb *et al.* (5)]. Not only were 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 whether 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

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without running the risk of altering peripheral innate immune cells at the same time. In addition, irradiating the head to deplete microglia results in a leaky blood-brain barrier, which facilitates the trafficking of cells and molecules normally having nothing to do in the brain. Godbout and his team opted instead to use 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). CSF1R is overexpressed on tumor-associated macrophages that play a pivotal role in tumor growth and immunotolerance, and therefore 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, McKim *et al.* (8) elegantly demonstrated that elimination of microglia abrogates recruitment of myeloid progenitor cells into the brain and blocks the development of anxiety. In a second series of experiments, the results of which are published in this issue of *Biological Psychiatry*, Weber *et al.* (9) used the same tool to investigate the relative importance of microglial and neuronal sensitization in the phenomenon of stress sensitization. Stress sensitization typically occurs when individuals who are 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 Weber *et al.* (9) 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 or 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 restimulation. Like macrophages, microglia are exposed to a wide variety of metabolic, homeostatic, and immune-regulatory signals in their microenvironment that 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 preexisting 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 Weber *et al.* (9) that are based on well-controlled psychosocial factors will ultimately help 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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Article Information

From the Department of Symptom Research, Unit 1450, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Address correspondence to Robert Dantzer, D.V.M, Ph.D., The University of Texas MD Anderson Cancer Center, Department of Symptom Research, 1515 Holcombe Dr, Houston, TX 77030; E-mail: rdantzer@mdanderson.org.

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References

1. Dantzer R (2018): Neuroimmune interactions: From the brain to the immune system and vice versa. Physiol Rev 98:477–504.
2. Pariante CM (2015): Psychoneuroimmunology or immunopsychiatry? Lancet Psychiatry 2:197–199.
3. Avitsur R, Stark JL, Sheridan JF (2001): Social stress induces glucocorticoid resistance in subordinate animals. Horm Behav 39:247–257.
4. Kinsey SG, Bailey MT, Sheridan JF, Padgett DA, Avitsur R (2007): Repeated social defeat causes increased anxiety-like behavior and alters splenocyte function in C57BL/6 and CD-1 mice. Brain Behav Immun 21:458–466.
5. Wohleb ES, Hanke ML, Corona AW, Powell ND, Stiner LM, Bailey MT, *et al.* (2001): β-Adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. J Neurosci 31:6277–6288.
6. Sherr CJ (1990): Colony-stimulating factor-1 receptor. Blood 75:1–12.
7. Chitu V, Gokhan S, Nandi S, Mehler MF, Stanley ER (2016): Emerging roles for CSF-1 receptor and its ligands in the nervous system. Trends Neurosci 39:378–393.
8. McKim DB, Weber MD, Niraula A, Sawicki CM, Liu X, Jarrett BL, *et al.* (2018): Microglial recruitment of IL-1beta-producing monocytes to brain endothelium causes stress-induced anxiety. Mol Psychiatry 23:1421–1431.
9. Weber MD, McKim DB, Niraula A, Witcher KG, Yin W, Sobol CG, *et al.* (2019): The influence of microglial elimination and repopulation on stress sensitization induced by repeated social defeat. Biol Psychiatry 85:667–678.
10. Glass CK, Natoli G (2016): Molecular control of activation and priming in macrophages. Nat Immunol 17:26–33.