Neuroinflammation: new vistas for neuropsychiatric research

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Abstract

In psychiatric diseases such as mood disorders or schizophrenia, the inflammatory response system is activated. Microglia has gradually emerged as a key interface between stress-related signals and neuroimmune consequences of stress, with stressors leading to elevated microglial activity.

Keywords: *inflammation; neuropsychiatric disorder; brain; microglia*

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Neuroinflammation is defined as inflammation of the nervous tissue. This inflammation may be initiated in response to a wide variety of stimuli, including infections, autoimmune or neurodegenerative disorders, traumatic brain injury, or stress. In the central nervous system, which was regarded as an immunologically privileged site because of the presence of the protective blood-brain barrier (composed of astrocytes and endothelial cells), immune functions are mediated by microglia, the resident innate immune cells, as well as by infiltrating immune cells. Although the neuroinflammatory response is initiated to exert protective effects, it may also exert detrimental effects and cause widespread inflammation through the blood–brain barrier. In fact, circulating peripheral immune cells may bypass an altered blood-brain barrier and come into contact with neurons and glial cells expressing major histocompatibility complex molecules, perpetuating the peripheral immune response. Even more, innate immune molecules such as complement proteins and cytokines regulate synaptic plasticity and neurogenesis, whereas amyloid-β and α-synuclein, biomarkers of neurodegenerative diseases, have antimicrobial roles. Type I interferons, for example, seem critical for normal neuronal homeostasis as a regulator of autophagy-mediated protein degradation, and T-cell cytokines IFN-g and IL-4 are involved in social and cognitive behavior. These findings suggest that, depending on the pathogen, host genotype or environmental factors, both pathogen and antipathogen pathways may affect interneuronal communication, leading to adaptive or maladaptive effects on brain function.[1] Thus, microglia is associated with clearance of cellular debris and toxicants, neurogenesis, and anti-inflammatory response, as well as synaptic monitoring and pruning. In turn, neurons play an important role in microglia function, by maintaining inflammatory gene production, oxidative stress response, and phagocytosis at an appropriate level, in order to keep their own homeostasis under normal physiological conditions. However, both neurons and microglia are sensitive to psychosocial stress, and chronic stress may impair the dynamic balance of neuron-microglia interaction, disturb synaptic neurotransmission, and thus increase the susceptibility to mental disorders. Similarly, aging also potentiates oxidative stress and neuroinflammation, leading to disturbances in synaptic monitoring and pruning functions, notably through defective phagocytosis.[2] Therefore, microglia has gradually emerged as a key interface between stress-related signals and neuroimmune consequences of stress, with different stressors leading to elevated microglial activity. The hippocampus and prefrontal cortex areas are especially involved.[3]

In psychiatric diseases such as mood disorders or schizophrenia, the inflammatory response system is activated[4] (see also Müller, in this issue p 55). The majority of studies have focused on antibodies, cytokines, and blood cell types (see also the rest of this issue). In addition, many epidemiological studies have implicated immune mechanisms as risk factors for developing schizophrenia: large odds ratios were reported for season of birth, maternal viral infection, cytokine alterations, and antibody/viral titer.[5] Accordingly, during the last decade, anti-inflammatory therapeutic approaches have been studied in schizophrenia and depression.

An extensive recent review of genetics in schizophrenia concluded that the most consistent result throughout the genome-wide association studies of schizophrenia is the association to the extended major histocompatibility complex locus located on chromosome 6p21.3 (MHC) or human leukocyte antigen (HLA) system.[6] This broad region comprises at least 121 functional genes. Significant MHC single-nucleotide polymorphisms associated, not only with schizophrenia, but also with bipolar disorder, cognition, or hippocampal volume have been reported.[7] Even more surprising, immune-mediated

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brain anomalies can be transmitted to subsequent generations providing interesting research avenues.[8]

Finally, Felger et al[9] have shown that an increase in inflammation, as demonstrated by plasma CRP and inflammatory cytokines, was associated with decreased connectivity within reward-related brain regions in unmedicated outpatients with major depression. In their study, decreased connectivity between ventral striatum and ventromedial prefrontal cortex (vmPFC) was correlated with symptoms of anhedonia, whereas decreased connectivity between dorsal striatum and vmPFC correlated with psychomotor slowing. Interestingly, in non-human primates, chronic administration of inflammatory cytokines decreased striatal dopamine release, as measured by translational neuroimaging and in vivo microdialysis.[10]

This issue will focus on the intriguing interplay between neuroinflammation and neuropsychiatric diseases. ❑

REFERENCES

1. Klein RS, Garber C, Howard N. Infectious immunity in the central nervous system and brain function. *Nat Immunol.* 2017;18(2):132-141.
2. Tian L, Hui CW, Bisht K. Microglia under psychosocial stressors along the aging trajectory: consequences on neuronal circuits, behavior, and brain diseases. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017 Jan 15. pii: S0278-5846(17)30035-0. doi: 10.1016/j.pnpbp.2017.01.007.
3. Calcia MA, Bonsall DR, Bloomfield PS, Selvaraj S, Barichello T, Howes OD. Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. *Psychopharmacology*. 2016;233:1637-1650.
4. Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. *Mol Psychiatry.* 2016;21(8):1009–1026.
5. Canetta SE, Brown AS. Prenatal infection, maternal immune activation, and risk for schizophrenia. *Transl Neurosci.* 2012;3:320–327.
6. Giegling I, Hosak L, Mössner R, et al. Genetics of schizophrenia: A consensus paper of the WFSBP Task Force on Genetics. *World J Biol Psychiatry.* 2017;Jan 23:1-14. Epub ahead of print.
7. Williams HJ, Craddock N, Russo G, et al. Most genome-wide significant susceptibility loci for schizophrenia and bipolar disorder reported to date cross-traditional diagnostic boundaries. *Hum Mol Genet.* 2011;20:387–391.
8. Weber-Stadlbauer U, Richetto J, Labouesse MA, Bohacek J, Mansuy IM, Meyer U. Transgenerational transmission and modification of pathological traits induced by prenatal immune activation. *Mol Psychiatry.* 2017;22(1):102-112.
9. Felger JC, Li Z, Haroon E, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Mol Psychiatry*. 2016;21(10):1358–1365.
10. Felger JC, Mun J, Kimmel HL, et al. Chronic interferon-alpha decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates. *Neuropsychopharmacology*. 2013, 38(11):2179–2187.