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The role of damage associated molecular pattern molecules (DAMPs) and permeability of the blood-brain barrier in depression and neuroinflammation

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Abstract

Depression is a heterogeneous mental disorder characterized by feelings of sadness and loss of interest that render the subject unable to handle basic daily activities such as sleeping, eating, or working. Neurobiological traits leading to depression include genetic background, early life abuse, life stressors, and systemic and central inflammatory profiles. Several clinical and preclinical reports documented that depression shows an increase in pro-inflammatory markers such as interleukin (IL-)1β, IL-6, IL-12, tumor necrosis factor (TNF), and interferon (IFN)-γ; and a decrease in anti-inflammatory IL-4, IL-10, and transforming growth factor (TGF)-β species. Inflammatory activation may trigger and maintain depression. Dynamic crosstalk between the peripheral immune system and the central nervous system (CNS) such as activated endothelial cells, monocytes, monocyte-derived dendritic cells, macrophages, T cells, and microglia has been proposed as a leading cause of neuroinflammation. Notably, pro-inflammatory cytokines disrupt the hypothalamic-pituitary-adrenal (HPA) axis and serotonergic, noradrenergic, dopaminergic, and glutamatergic neurotransmission. While still under investigation, peripheral cytokines can engage brain pathways and affect the central synthesis of HPA hormones and neurotransmitters through several mechanisms such as activation of the vagus nerve, increasing the permeability of the blood-brain barrier (BBB), altered cytokines transport systems, and engaging toll-like receptors (TLRs) by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). However, physiological mechanisms that favor time-dependent central inflammation before or during illness are not totally understood. This review will provide preclinical and clinical evidence of DAMPs and the BBB permeability as contributors to depression and neuroinflammation. We will also discuss pharmacologic approaches that could potentially modulate DAMPs and BBB permeability for future interventions against major depression.