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Perspective

Therapeutic Strategies Targeting Chronic Inflammation and its Role in Neurodegenerative Diseases

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ABOUT THE STUDY

Neurodegenerative Diseases (NDs) are a group of disorders characterized by the progressive degeneration of the structure and function of the nervous system. These diseases, includes Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), and Amyotrophic Lateral Sclerosis (ALS), often result in debilitating symptoms such as memory loss, motor dysfunction, and cognitive decline. While the exact causes of these diseases remain largely elusive, one emerging factor that has gained significant attention is chronic inflammation. Inflammation, a natural immune response to injury or infection, can become chronic in certain conditions, leading to tissue damage and contributing to the pathogenesis of neurodegenerative diseases.

Understanding chronic inflammation

Inflammation is a protective response of the immune system that is triggered in response to harmful stimuli such as pathogens, damaged cells, or irritants. It is a complex process involving the activation of immune cells, the release of inflammatory mediators, and changes in blood flow. While acute inflammation is a protective response aimed at healing, chronic inflammation occurs when this process persists over an extended period, often in the absence of an acute trigger.

In the Central Nervous System (CNS), chronic inflammation is primarily mediated by microglia, the resident immune cells of the brain and spinal cord. Microglia play an important role in maintaining the homeostasis of the CNS, but when activated by various stimuli, they release pro-inflammatory cytokines, Reactive Oxygen Species (ROS), and other mediators that can cause neuronal damage.

Role of chronic inflammation in NDs

Chronic inflammation has been implicated in several neurodegenerative diseases, including AD, PD, and ALS. The following sections explore how inflammation contributes to the pathogenesis of these diseases.

AD: It is the most common form of dementia, characterized by the progressive loss of memory and cognitive function. One of the hallmark features of AD is the accumulation of amyloid-beta plaques in the brain. These plaques trigger an inflammatory response in the brain, primarily mediated by microglia. Under normal conditions, microglia attempt to clear amyloid-beta aggregates, but in AD, microglia become chronically activated, leading to the release of pro-inflammatory cytokines, such as Interleukin-1 (IL-1), Tumor Necrosis Factor-alpha (TNF-α), and Interleukin-6 (IL-6).

PD: It is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as tremors, rigidity, and bradykinesia. Although the exact cause of PD remains unknown, growing evidence suggests that chronic inflammation plays a central role in its pathogenesis. In PD, microglia in the substantia nigra become activated in response to the accumulation of misfolded alpha-synuclein, a protein that forms toxic aggregates in the brains of PD patients.

ALS: It is a progressive NDs that affects motor neurons, leading to muscle weakness, paralysis, and ultimately, respiratory failure. Inflammation has been implicated in ALS, with evidence suggesting that microglial activation and the release of inflammatory cytokines contribute to motor neuron death. In ALS, microglia become activated in response to the accumulation of misfolded proteins, such as Superoxide Dismutase 1 (SOD1) aggregates, which are commonly found in familial ALS.

Mechanisms of chronic inflammation in NDs

The chronic inflammation observed in NDs is prompted by a variety of mechanisms, including the activation of innate immune cells, the release of inflammatory mediators, and the dysregulation of immune signaling pathways.

Microglial activation: Microglia are the primary immune cells in the CNS, and their activation is a key feature of chronic neuroinflammation. Under normal conditions, microglia are in a resting or surveillant state, constantly monitoring the brain for

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signs of injury or infection. When microglia detect abnormal signals, such as the presence of misfolded proteins, they become activated and initiate an inflammatory response.

Inflammatory mediators: Including cytokines, chemokines, and ROS, play a central role in the neuroinflammatory process. Cytokines such as TNF-α, IL-1β, and IL-6 are elevated in the brains of individuals with NDs and contribute to neuronal damage by promoting oxidative stress, excitotoxicity, and apoptosis.

Dysregulation of immune signaling pathways: In NDs, there is often a dysregulation of immune signaling pathways, which leads to sustained inflammation. For example, the activation of the Nuclear Factor kappa B (NF-κB) pathway, which is a central regulator of inflammation, is elevated in the brains of individuals with AD and PD. The prolonged activation of this pathway promotes the production of pro-inflammatory cytokines and ROS, creating a cycle of inflammation that accelerates neurodegeneration.

Therapeutic strategies targeting chronic inflammation

Given the central role of chronic inflammation in NDs, targeting inflammation has become a potential therapeutic strategy. Several approaches are being investigated to modulate the inflammatory response in the brain, including the use of anti-inflammatory drugs, immunomodulatory therapies, and lifestyle interventions.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): These are commonly used to reduce inflammation in various conditions. Some studies have suggested that NSAIDs may have neuroprotective effects in NDs by inhibiting Cyclooxygenase enzymes (COX-1 and COX-2), which are involved in the production of pro-inflammatory prostaglandins.

Immunomodulatory therapies: Aim to modulate the immune response to reduce inflammation without suppressing the immune system entirely. For example, drugs that inhibit the NF-κB pathway or the inflammasome pathway have shown potential in preclinical models of NDs.

Chronic inflammation is a key factor in the pathogenesis of NDs. The persistent activation of microglia and the release of pro-inflammatory mediators contribute to neuronal damage, accelerating the progression of diseases such as AD, PD, and ALS.