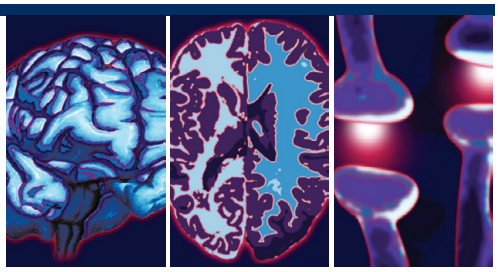
Perspective



Pro-Inflammatory Cytokines released by Microglia in Alzheimer's Disease

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Introduction

Alzheimer's Disease (AD) is a complex, chronic neurodegenerative disorder that affects adults over the age of 65 and causes a significant burden on those who are affected, their families, and society. Pathological features of Alzheimer's disease include extracellular deposition of -Amyliod (A) and intracellular neurofibrillary tangles, both of which are thought to play a role in the illness's development. Synaptic dysfunction, mitochondrial damage, microglia activation, and neuronal death are all caused by tau protein deposition. However, it is becoming clear that neuro inflammation cascades mediated by primed microglia cells have a role in the aetiology of Alzheimer's disease. A wealth of research relating the pro-inflammatory cytokines [such as IL-1, IL-6, and Tumour Necrosis Factor (TNF-)] produced by microglia and their role in AD has recently gained great attention.

Microglia, the most numerous immune cells in the Central Nervous System (CNS), have long been a hotspot in Alzheimer's disease (AD) research due to their dramatic responses to the illness's pathogenesis. Microglia activation has two consequences on Alzheimer's disease progression: On the one hand, it reduces a build up by enhancing phagocytosis, clearance, and degradation, preventing the production of amyloid plaques in the brain. Prolonged microglia activation, on the other hand, causes the release of pro-inflammatory cytokines, which triggers a pro-inflammatory cascade and adds to neuronal damage and death. We review recent findings of pro-inflammatory cytokines generated by microglia, hypothesise on their likely role in AD progression, and discuss current advances and problems in targeting pro-inflammatory cytokines for AD therapy in this article.

Pro-Inflammatory Cytokine Dysregulation in the Brain

Increased production of pro-inflammatory cytokines including as TNF-, IFN-, IL-1, IL-6, and IL-18, as well as activation of their corresponding receptors, have been shown in the AD brain in both experimental and clinical studies. However, there has been research on the relationships between pro-inflammatory cytokines and senile plaques, a key hallmark of Alzheimer's disease. Chronic A deposition in the brain activates microglia, which is thought to be a significant source of pro-inflammatory cytokines in Alzheimer's disease.

A binding to the microglial cell surface triggers pro-inflammatory gene expression and increases pro-inflammatory cytokines such TNF-, IL-1, IL-6, and IL-18, leading to tau hyper phosphorylation and neuronal death. Furthermore, research found that transcript levels for a number of pro-inflammatory markers like TNF and IL-1 were higher in AD, notably in response to tau. Chronic inflammation, as previously mentioned, could be a result of AD pathogenesis, exacerbating the harmful effects of A

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and tau.
This view has been called into doubt, and fresh evidence suggests that an increase in A and tau phosphorylation in the brain could be a cause of Alzheimer's disease. A prior study found that generating neuro inflammation in transgenic mice by injecting LPS caused intracellular A deposition and tau phosphorylation in the brain. However, earlier research has suggested that pro-inflammatory cytokines and A can have synergistic effects, with IFN- triggering the generation of TNF- and reactive nitrogen species, both of which are toxic to neurons.

The expression of pro-inflammatory cytokines by non-neuronal cells in the AD brain, particularly endothelial cells, is thought to have a role in the disease's progression. Pro-inflammatory cytokines such as TNF-, IL-1, and IL-6 are released at much higher levels in AD brain micro vessels than in age-matched controls. Inflammation precedes A deposition, which stimulates the production of inflammatory mediators, and the cerebral microvasculature is involved in this damaging cycle. In this case, A causes a cascade of pro-inflammatory responses in brain endothelial cells.

This is substantiated by the observation that A1-40 increases the expression of inflammatory genes IL-1 and IL-6 in cultured human brain endothelial cells, as confirmed by quantitative RT-PCR analysis. These findings imply that the cerebral microcirculation provides pro inflammatory cytokines to the AD brain's environment and may play a role in the disease's pathogenesis of neuronal injury and death.

Furthermore, some studies suggest that chronic inflammation in the peripheral can cause pro-inflammatory cytokines to breach the Blood-Brain Barrier (BBB) and contribute to cognitive impairment in Alzheimer's patients by causing pro-inflammatory cytokines in the CNS. Indeed, Capron and Miller recently evaluated the mechanisms for pro-inflammatory cytokines to get from the bloodstream to the brain.

Furthermore, A could traverse the BBB from the periphery into the brain, mediated via RAGE. Furthermore, A binding to RAGE on microglia allowed for persistent activation and inflammatory response, resulting in a rise in pro inflammatory cytokines. In the United States, research has revealed that A-related BBB leakage may be present in patients with cerebral amyloid antipathy, which affects the majority of AD patients. Based on these findings, brain pro-inflammatory cytokines could be regarded a biomarker for Alzheimer's disease.

Targeting the increased circulation levels of pro inflammatory cytokine IL-1 with a neutralising antibody drastically reduced the activity of multiple tau kinases and levels of phosphorylated tau (p-tau), as well as the load of oligomer and Fibrillar A (fA) in triple-transgenic mouse models of AD. As a result, any major inflammatory response inside the brain tissue appears to be linked to pro-inflammatory cytokine malfunction, presenting the possibility of using pro-inflammatory cytokines as a surrogate marker for a local inflammatory response in AD.