

Letter to Editor



Neuroinflammation alleviation

Seyed-Amirabbas Ahadiat^{1*}, Zeinab Hosseinian¹¹Department of Bimolecular and Biomedicine, University of Girona, Girona, Spain*Corresponding Author: Seyed-Amirabbas Ahadiat, Email: Dr.ahadiat61@gmail.com

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Dear Editor,

Aging is a significant risk factor for several neurodegenerative diseases (1,2). It is estimated that neurological disorders lead to more than 6.8 million deaths annually (3). However, the therapeutic options effective for age-related neurodegenerative diseases are limited (4). In addition, the current treatments for these diseases are associated with high economic burdens on society and affected patients. The average annual cost of treatment for neurological disorders in Europe varies from 285 euros for headaches and 30 000 euros for neuromuscular disorders. Further, neurodegenerative diseases are highly prevalent and typically have an irreversible progression (5).

According to evidence, these diseases are associated with the pathological aggregations of different proteins. Generally, proteins play an essential role in cellular structure and function, while their activities result from their amino acid sequence and spatial configuration. The proper action of proteins is vital for the optimum function of body systems (6).

Each neurodegenerative disease is characterized by the accumulation of a specific protein, and protein aggregates represent the characteristic pathological lesions of these diseases. Furthermore, it has been shown that the proteins aggregated in these diseases have structural abnormalities such as α -synuclein in Parkinson's disease and TAR DNA-binding protein 43, the most common protein associated with amyotrophic lateral sclerosis (7). For instance, the pathophysiology of Alzheimer's disease (AD) is hypothesized to be the amyloid and tau overproduction and amyloid cascade. Based on this hypothesis, A β accumulation is the initial cause that triggers an overflow of effects, ultimately leading to neurodegeneration (8).

On the other hand, bringing preclinical therapies to clinical practice is a significant challenge in neuroscience. Up to now, no clinically successful medication has been approved for managing neurodegenerative disorders due to the lack of reliable drug targets.

Neuroinflammation is generally caused by various pathological conditions such as infection, trauma,

ischemia, and toxins. Prolonged inflammation may cause microglia to produce neurotoxic agents, leading to the enhancement of tissue damage. This process leads to the release of proinflammatory cytokines, including *interleukin* (IL)-1 β , IL-6, IL-18, and *tumor necrosis factor* (TNF), as well as chemokines such as CCL1 and CCL5. In addition, microglia and astrocytes are the main cells of the innate immune system involved in this process. However, capillary endothelial and infiltrating blood cells also contribute to neuroinflammation, especially in the case of biochemical or mechanical damage to the blood-brain barrier (9,10). During inflammation, the secretion of pro-inflammatory substances can lead to synaptic malfunction, apoptosis, and inhibition of neurogenesis.

Under normal and pathological conditions, glial cells produce anti-inflammatory substances such as IL-1, IL-4, IL-10, and IL-11. Moreover, they are involved in phagocytosis, steroid release, cytokine release, free radical scavenging, and cell repair. However, their activity may damage the intact neurons, leading to synaptic dysfunction, synaptic loss, and neuronal death (11). As a result, an imbalance between the pro-inflammatory cytokine release and neuronal restorative functions may lead to damage to the central nervous system (CNS). It has been reported that several neurodegenerative diseases are associated with the neuroinflammation and activation of neuroimmune cells, including microglia and astrocytes (12,13). According to a study by Liu et al (14), alleviating the neuroinflammation in the preclinical stage of AD may be a highly effective strategy for AD treatment and prevention. Furthermore, Leitner et al (15) reported that the antagonists of Toll-like receptor 4 may improve CNS diseases associated with neuroinflammation by reducing the levels of inflammatory mediators.

Phosphoinositide-3-kinases (PI3Ks) are a group of enzymes that regulate a variety of activities such as signaling and cell proliferation. PI3K signaling has been found to coordinate an array of events that regulate inflammatory reactions in activated microglia, which, in turn, can impair cell survival in healthy and diseased states

such that the function of PI3K enzymes has consequences for neuronal physiology in both healthy and sick states. Therefore, the modulation of PI3K could become a potential therapeutic strategy (16,17).

The production of reactive oxygen species (ROS) occurs as a result of mitochondrial oxidative metabolism, as well as cellular responses to xenobiotics, cytokines, and bacterial invasion. As a result of the mitochondrial leakage of superoxide, hydrogen peroxide (H₂O₂) contributes to oxidative damage. Due to the increase of ROS, the accumulation of the A42 protein in microglia causes oxidative damage to the brain. Oxidative damage causes cell disorders and plays a role as a strong factor in the pathogenesis of diseases such as diabetes and stroke, and regulates calcium levels to prevent neuroinflammation. In their study, Li et al could reduce A42 protein aggregation and oxidative damage by nanoparticles under 808 nm laser irradiation. Additionally, these nanoparticles reduced the concentration of Ca²⁺ and TNF- α by inhibiting the melastatin receptor potential 2 ion channel inside the cell. In this study, they proposed a therapeutic strategy to reduce neuroinflammation by simultaneously regulating ROS and Ca²⁺ signals (18).

In conclusion, inflammation may play an important role in neurodegenerative diseases. Therefore, alleviating neuroinflammation may be a potential therapeutic option for these diseases.

Authors' Contribution

Conceptualization: Seyed-Amirabbas Ahadiat.

Investigation: Zeinab Hosseinian, Seyed-Amirabbas Ahadiat.

Supervision: Zeinab Hosseinian.

Validation: Zeinab Hosseinian.

Visualization: Zeinab Hosseinian.

Writing—original draft: Seyed-Amirabbas Ahadiat, Zeinab Hosseinian.

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