Astrocyte as the Modulator in Brain Inflammation and Neurodegenerative Disorders

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The central nervous system (CNS) consists of neurons and neuroglial cells. Among neuroglial cells in the adult human brain, astrocytes constitute most (approximately 40%) of cell population, and maintain homeostasis in normal CNS. Many reports indicate that astrocytes participate in various functions including guidance of the neuronal development and migration during CNS development, supporter of neuronal growth, preservation of the integrity of the blood-brain barrier (BBB), and playing a part in the immune responses to brain injury or disorders [1]. Moreover, as well as microglia, astrocytes display various receptors participated in innate immunity, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domains, double-stranded RNA-dependent protein kinase, mannose receptor and components of the complement system [2]. One common feature of various neurodegenerative diseases is activation of large number of astrocytes and microglia that includes the morphological changes and expression of many inflammatory mediators. Astrogliosis is characterized by astrocytic proliferation, hypertrophy of the cell body, and functional changes, when exposed to various factors including interleukin-1β (IL-1β), tumor necrosis factor (TNF)-α, and lipopolysaccharide (LPS) [3].

Accumulating studies have indicated that the cell-cell interactions between glial cells and neurons is important in the regulation of brain inflammation and neurodegeneration. Recent reports also implicate that inflammation contributes to a wide variety of brain pathologies, apparently killing of neurons via glia [1]. Thus, the activated glial cells are indicated to play a critical role in the progression and pathogenesis of neurodegeneration. Previous most reports have shown that microglial cells may be a major inflammatory cell of the brain [4]. The activated microglia produce several inflammatory mediators including cytokines or cytotoxic molecules, including interleukin-1β (IL-1β), tumor necrosis factor (TNF)-α, and lipopolysaccharide (LPS) [3].

Inflammation is a natural protective reaction to various cell and tissue injury. The purpose of this process is to remove the detrimental agents and injured tissues, thereby benefiting tissue repair. When this helpful reaction is uncontrolled, the effect initiates extravagant cell and tissue damage that results in normal tissue destruction and chronic inflammation [8]. Moreover, the brain neurodegenerative diseases, including Alzheimer’s disease (AD) and Parkinson’s disease (PD), are characterized by intracellular signaling state imbalance and chronic neuroinflammation, a major cause of cell damage and death. Several of the well-known inflammatory mediators such as matrix metalloproteinases (MMPs) or COX-2/PGs are associated with diverse signaling molecules activated by pro-inflammatory factors such as cytokines, peptides, pathogenic structures (e.g., bacteria or virus), and per-oxidants in rat brain astrocytes [6]. Moreover, recent data also indicated that multiple factors from BK-challenged brain astrocytes may contribute to the neuronal cell apoptosis [7]. These results implicate that activated neuroglial cells, astrocytes especially, play a critical role in the brain inflammatory response leading to neurodegenerative disorders.

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susceptible to the injurious effects of various stresses. Several studies have shown that brain cells like microglia and astrocytes induce and release diverse inflammatory mediators in response to pro-inflammatory factors [1,10]. In the CNS, following the stimulation of pro-inflammatory factors, integration of various signaling molecules to trigger inflammatory responses through activation of different transcription factors, including nuclear factor-kB (NF-kB) and activator protein-1 (AP-1) [1,10]. Here, we focus on many general aspects of pro-inflammatory signaling molecular regulation, their involvement in the expression of inflammatory target proteins, and the effects of these signals on the brain neuroinflammation. Therefore, the inhibition of the expression of inflammatory target proteins (e.g., MMP-9)-mediated inflammatory pathways may provide therapeutic strategies to brain neuroinflammation and neurodegenerative diseases.

Brain glial cells maintain CNS plasticity and protect the brain for functional repair from injuries. Reactivation of glial cells may promote neuroinflammation and neurodegeneration and, ultimately, the retraction of neuronal synapses, which leads to cognitive deficits [1]. Moreover, up-regulation of these inflammatory mediators is a deleterious event in several inflammatory diseases such as AD that precedes the formation of these disease pathologies. To date, although numerous effects have been made to develop therapies based on signaling molecules or target mediators in the past years, the actual benefits to the patients have been very limited. It may be due to lack of potency, late administration and poor penetration into the brain cells [11]. Alternative strategies including searching for pro-inflammatory factors that induce inflammatory mediators via diverse signaling pathways are necessary to improve the efficacy of treatment. Hence, understanding what pro-inflammatory factors participate in these inflammatory mediators expression and the regulating mechanisms that might help to develop effectively therapeutic strategies for the CNS diseases.

First, we focus on glial cells, in particular astrocytes, and their effects on the CNS disorders. Next, we summarized the interplay between these inflammatory mediators and neuroinflammation by action of various pro-inflammatory factors contributes to neurodegeneration, thereby enhancing disease progression based on data collected from brain cells, particularly astrocytes, in in vitro and in vivo studies. Perhaps by retarding the activation of glial cells to decrease their neurotoxic properties and enhance their neuroprotective effects may offer potential targets for therapeutic interventions in CNS degenerative disorders. Previously, pro-inflammatory factors-induced signaling transduction pathways, including Ca2+-related signals, PKCs, ROS, transactivation of PDGFR, PI3K/Akt cascade, MAPKs, NF-κB, and AP-1 that are associated with the CNS disorders were investigated in brain astrocytes. Possible therapeutic strategies to target signaling molecules, transcription factors, or inflammatory mediators are implicated based on many updated view of pro-inflammatory factors-mediated regulation of various inflammatory mediators in brain inflammation and neurodegenerative disorders.

REFERENCES