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Progress in the Role of Microglia Mediated Inflammatory Response in Brain Injury Induced by Ischemia-Reperfusion

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Abstract

Cerebral ischemia reperfusion injury is a complex pathophysiological process involved in various mechanisms, in which inflammatory response is the main link to induce ischemic injury. After cerebral ischemia reperfusion injury, the inflammatory mediators IL-1, IL-6, TNF-alpha and ICAM-1 in ischemic brain tissue increased significantly. A variety of signaling pathways in are involved in inflammatory responses, such as PI3K/Akt, TLR4/NF-κB, MAPK, and JAK/STAT signaling pathway. The relationship between signal pathways to fully elucidate the cerebral ischemia reperfusion injury and microglia mediated, help to further understand the mechanism of microglia and cerebral ischemia reperfusion injury, and provide a theoretical basis for a new target for more effective.

Keywords: Ischemia-reperfusion; Brain injury; Inflammation; Microglia; Alpha 7-nAChR

Introduction

Ischemic cerebrovascular disease accounts for 80% of all cerebrovascular disease, with high incidence, high morbidity, high mortality, high disability rate, high recurrence rate, has become one of the three major diseases serious harm to human health [1]. Due to the lack of effective treatment, rehabilitation measures, reasonable prevention and how to alleviate the early brain damage, it has become the current research hotspot. Previous studies have shown that many factors are involved in the pathogenesis of ischemic stroke, at present, it is gradually believed that inflammation is a mechanism that plays an important role. Microglia is thought to be the main initiator and participant in the brain inflammatory response. After cerebral ischemia, activated microglia can not only play neuroprotective effect, but also produce neurotoxic effects. Therefore, the role of microglia in cerebral ischemia injury is controversial. Further study on the role of microglia in cerebral ischemia injury will provide new ideas and approaches for the clinical treatment of cerebral ischemia injury. This article will discuss how microglia mediates inflammatory response and the role of microglia in the progression of brain injury induced by ischemia and reperfusion.

Brain Injury Induced by Ischemia Reperfusion

Cerebral ischemia and reperfusion indicate that the initial cerebral blood supply is limited, and then the blood flow is restored and reoxygenation [2,3]. After cerebral ischemia for a certain period of time, the function of the blood supply not only failed to recover, but also appeared more serious brain dysfunction, called cerebral ischemia reperfusion injury (CIR). The specific mechanism of CIR is unknown, which may be related to the toxins produced by oxygen free radicals, calcium overload, destruction of mitochondrial structure and function, inflammatory response, lack of high-energy phosphate compounds, energy metabolism, apoptosis, and so on [4,5]. It is worth noting that inflammatory reaction and apoptosis play an important role, and are the main link of nerve cell injury induced by ischemia reperfusion. These mechanisms overlap and interact with each other, forming a vicious circle, eventually causing apoptosis or necrosis, resulting in irreversible damage to the brain tissue in ischemic areas. Therefore, how to inhibit the inflammatory response and apoptosis after CIR is of great significance.

Inflammatory Response and Inflammatory Mediators

Inflammatory response refers to the migration of the fluid in the microcirculation and immune cells from the blood vessels to the tissues, and the independent damage, protection, and repair of tissue is the main reaction. The inflammatory cascade after ischemia is initially caused by hypoxia, resulting in metabolic failure leading to controlled cell death [6]. Cell debris produced by cell death and cytokines secreted by damaged cells, adenosine triphosphate(ATP), uric acid, reactive

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oxygen species (ROS) [7,8] and other dangerous signals, stimulate inflammatory response. Although these dangerous signals are essentially different, they are similar to the fusion of local immune cells, to stimulate production and secretion of pro-inflammatory cytokines. Tumor necrosis factor (TNF- alpha) [9], interleukin -10 [10] and matrix metalloproteinases [11], intercellular adhesion molecule -1 (ICAM -1) [12] and chemokine [13] are important inflammatory mediators in cerebral ischemia, which may cause ischemic inflammation.

Microglia and Inflammatory Response in the Brain

Brain injury caused by ischemia reperfusion is accompanied by local excessive inflammatory response, which is one of the main causes of reperfusion injury. Many inflammatory cells and inflammatory mediators are involved in the inflammatory response [14]. Tzeng et al. [15] showed that the activated glial cells are mainly astrocytes and microglia after injury of central nervous system, and microglia are the earliest cells to respond to the injury of central nervous system [16]. Activation of microglia is a marker of inflammation. Microglia is the smallest glial cells in the central nervous system, which account for about 5% ~ 20% of all glial cells. Microglia, a phagocye that settles in the brain, is widely distributed in the central nervous system, and is distributed in all regions of the brain. Normally, resting microglia are not dormant, but dynamically monitor their microenvironment by projecting elongated projections [17], and monitor synaptic function by synaptic contact [18]. Microglia is the major phagocytic cells in the central nervous system, and microglia is responsible for the balance of body by phagocytosis of debris and apoptotic neurons [19]. Resting microglia is activated after brain injury. One of the characteristics of damage induced microglial activation is that the number of resident cells reaches a peak 48-72h after injury [20]. Activated microglia play a neuroprotective and neurotoxic effects, on the one hand, phagocytosis of cellular debris and harmful substances, the release of anti-inflammatory factors, thus weaken the adverse effects of inflammation and promote tissue recovery; on the other hand, producing reactive oxygen species and inflammatory cytokines, which play a cytotoxic role [21]. What specific function of microglia is determined depends on whether the neurons and astrocytes around transmit specific signals to them [22]. Therefore, although moderate activation of microglia can alleviate metabolic disturbances in tissues or cells and promote tissue repair, excessive activation can lead to the release of large amounts of free radicals and pro-inflammatory cytokines, which mediate oxidative stress and inflammatory response. In conclusion, microglial activation and proliferation are characteristics of many central nervous system injuries. However the potential molecular mechanisms underlying the regulation of microglial activation and proliferation after injury are still unknown.

Girard et al found BM macrophages and BV-2 microglia can differentiate into two subtypes of M1 or M2 after LPS or IL-4 stimulation [23]. M1, a classical activation type, is not only an effector cell of innate immunity, but also an effector cell that adapts to immunity. NF-kB transcription is active in M1 microglia, which produce and release a large number of pro-inflammatory cytokines(such as IL-1 beta, IL-6, IL-23 and TNF- alpha, triggering inflammatory response), cytotoxic substances (such as oxygen free radicals, NO and so on, produce oxidative stress damage), and proteolytic enzymes (MMP9, MMP3 and so on, act on extracellular matrix and destroy blood brain barrier) [24]. M2 is selective activation type, with the phagocytic function, producing anti-inflammatory effects through the release of IL-4, IL-10, IL-13, TGF-beta, IGF-1 and other factors, or through the release of extracellular matrix proteins promoting tissue repair [25]. Therefore, microglia mediated immune response is multifaceted and complex after cerebral ischemia.

The Effect of Intervention Inflammatory Response on Ischemic Brain Injury

Inflammation may aggravate the deterioration in the early stage of ischemic brain injury. If it can effectively block the harmful inflammatory response, and promote the protective effect of inflammatory response, therefore, it will contribute to the relief and prognosis of cerebral ischemia. Although large number of inflammatory mediators may damage neurons, regulation of microglia mediated inflammatory response may play a neuroprotective role [26]. Ischemic brain injury modulates inflammatory response through cholinergic anti-inflammatory pathway. The cholinergic anti-inflammatory pathway refers to the pathway that the central nervous system regulates or inhibits inflammation through cholinergic nerves and their transmitters. Interaction of acetylcholine released from vagus nerve endings and alpha 7 nicotinic acetylcholine receptor (a 7-nAChR) from cholinergic terminals of tissue macrophages and other immune cells, can inhibit the synthesis or release of inflammatory cytokines, to reducing the level of cytokines in plasma, and reducing the inflammatory response.

Effect of alpha 7-nAChR on Inflammatory Response of Microglia

Although the alpha 7-nAChR was originally found in neurons, but later in T lymphocytes, B lymphocytes, dendritic cells, monocytes, neutrophils, microglial cells, epithelial cells and endothelial cells [27], and almost all alpha 7-nAChRs in these cells are directly involved in anti-inflammatory. Therefore, the anti-inflammatory mechanism mediated by the alpha 7-nAChR is essential for the regulation of inflammatory response. Using the alpha bungarotoxin (alpha -7nAChR antagonist) blockade of alpha-7nAChR or alpha7- subunit gene knockout mice, mice were found to be extremely sensitive to inflammation, with elevated levels of pro-inflammatory cytokines [28], So it is proved that alpha-7nAChR is a molecular core mediated neurogenic inflammatory pathway.

Intracellular Signaling Pathways Associated with Inflammatory Response in Microglia

PI3K/AKT signaling pathway: Previous studies have demonstrated that PI3K/AKT is activated and involved in stress response during cerebral ischemia [29,30]; The regulation of PI3K/AKT pathway may reduce brain injury induced by cerebral ischemia reperfusion [31]. Studies have shown that in mice with alpha-7nAChR deletion mutations, nicotine protects neurons from Ca^{2+}-CaM -PI3K signaling pathways by inhibiting [32].

TLR4/NF-κB signaling pathway: Endogenous molecular release can be induced by ischemic brain injury, and combined with microglial cells TLR4, the activation of TLR 4 leads to nuclear translocation of NF-κB, inflammatory response are induced by the expression of inflammatory mediators [33]. Therefore, activation of TLR4/NF-κB signaling pathway in microglia may be an important cause of brain damage aggravation.

MAPK signaling pathway

Mitogen activated protein kinase (MAPK) signal transduction

pathway is an important pathway related to microglia function, mainly including ER K1/2, p38MAPK, JNK three pathways. Nam et al studies have found that inhibition of ERK 1/2 pathway can attenuate microglia inflammatory response [34]. Wang et al. [35] studied microglia cell line BV-2 cells and found that LPS induced microglial activation by activating p38 signaling pathway, using p38 inhibitor SB202190 or SB20358 can inhibit the release of cytotoxic factors (such as TNF-alpha, iNOS, NO) by activated microglia, which plays a protective role in neurons. JNK is composed of JNK 1, JNK 2 and JNK 3 and the expression of JNK 1 and JNK 2 is extensive, while the expression of JNK 3 is confined to brain tissue. JNK is an important mediator of microglia in inflammatory response, and different JNK subtype exerts different functions. JNK signaling pathway can regulate the expression of a variety of inflammatory protein genes and participate in immune response, inflammatory response [36].

JAK/STAT signaling pathway: Kim et al found that JAK/STAT signaling pathway mediates the activation of microglia stimulated by gangliosides, it is one of the fastest reaction pathways when inflammation occurs [37]. In microglia, curcumin inhibits the inflammatory response of microglia by inhibiting the JAK/STAT signaling pathway by activating SHP-2 [38].

Inflammatory reaction runs through the whole pathological process of ischemic brain injury, is one of the main factors affecting the prognosis. Microglia plays an important role in delayed neuronal death induced by inflammation. Many signal pathways in microglia are involved in inflammatory response, and PI3K/AKT signaling pathway is one of the classic signaling pathways in cells, and plays an important role in cell growth, adhesion, differentiation and inflammatory response. Alpha 7-nAChR is involved in various neuroprotective and inflammatory mechanisms [39], which are closely related to ischemic brain damage. Previous study found that nicotine inhibits expression of TNF-alpha and IL-1 beta in ischemic brain region [40], but the exact molecular mechanisms underlying nicotinic inhibition is still not clear. In view of the fact that PI3K/Akt signal pathway and alpha 7-nAChR are closely related with inflammatory reaction, PI3K/AKT signaling pathway may play an important role in nicotine inhibits microglial inflammatory reaction.

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