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Physiological Study of Microglial Cell Polarization

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Abstract: Microglia play an important role in the course of ICH (Intracerebral Hemorr-Hage), and its activation degree, phenotypic polarization, hematoma clearance mechanism and its interaction with nerve cells are hot topics in ICH research at present. In this paper, ICH was taken as an example, and the research progress of microglia function changes after ICH was summarized, and the phenotypic transformation of microglia was summarized. The nitrite peroxide produced by M1 microglia in the immune reaction externalizes the phosphoacyl serine residues outside the nerve cells and sends out phagocytic signals, so that microglia can play the role of brain phagocytosis and cause nerve cell damage. The expression of pro-inflammatory microglia (M1 type) and repair microglia (M2 type) increased, and the microglia were mainly M1 type. In addition, the expression of M1 microglia in ICH 72 h group was lower than that in ICH 24 h group, while the expression of M2 microglia in ICH72 h group was higher than that in ICH 24 h group. Compared with Sham group, the increasing trend of M1 microglia expression after ICH is consistent with the increasing trend of TLR4/NF-κ B.

1. Introduction

Microglia are inherent immune cells in the brain, which have the functions of nourishing, protecting, and repairing nerve cells. They are also the first line of defense of the central nervous system against various types of damage, and are closely related to the pathogenesis of many neurodegenerative diseases and inflammatory diseases in the brain. Taking cerebrovascular diseases as an example, cerebrovascular diseases are a serious threat to human health and life safety, and have become the third leading cause of death in the world. ICH, also known as intracerebral hemorrhage, refers to the rupture of blood vessels in the brain caused by non-traumatic factors, which in turn causes blood to accumulate in the brain parenchyma, leading to corresponding neurological deficits [1]. The high incidence rate and disability rate of ICH have caused a heavy burden to society and families. In the early stage of ICH, primary brain injury causes hematoma compression and edema around the hemorrhagic focus, resulting in a space occupying effect and intracranial hypertension, leading to brain hernia formation and death. After that, microglia are activated, inducing the secretion of various proinflammatory factors, promoting oxidative stress and cytotoxic cascade reactions, leading to functional damage and death of nerve cells, ultimately leading to secondary brain injury [2].

The first step in the inflammatory response in the brain is the activation and polarization of microglia, which in turn initiates the release of effector molecules and other immune cells. Therefore,

reducing the excessive activation of microglia and reducing the release of inflammatory factors is an important means to prevent and treat the above-mentioned central nervous system diseases [3]. Primary brain injury and secondary brain injury after ICH are two major pathophysiological mechanisms leading to impairment of neural structure and function. However, after ICH modeling, one side of the brain tissue of the rats was damaged, resulting in paralysis of the opposite limb and inability to stand and turn, so the number of times to the cerebral infarction side would significantly increase. Among them, secondary injury plays a crucial role in nerve injury after ICH. Activated microglia promote nerve regeneration and tissue repair by releasing neurotrophic factors and anti-inflammatory factors to remove toxic substances or invasive pathogens. Microglia are key innate immune cells and are the first non neurons to respond to various pathophysiological mechanisms of acute brain injury. After activation, they can secrete chemokines, cytokines, prostaglandins, and other immunomodulatory molecules, which play an important role in secondary brain injury and brain repair [4-5].

This article aims to summarize the research progress in the functional changes of microglia after ICH, especially focusing on the activation, polarization, proliferation, secretion, and phagocytosis of microglia, and summarize the phenotypic changes of microglia. Although many mechanisms of microglial cell polarization after ICH are still unclear, some experimental drugs have proven that they can alleviate secondary brain injury and promote the recovery of neural function by inhibiting M1 type polarization or enhancing M2 type polarization. After cerebral ischemia, the different polarization phenotypes of microglia can play a proinflammatory or anti-inflammatory role. Overactivated microglia produce neurotoxicity by releasing some toxic substances, which can lead to "secondary injury" of neurons [6]. However, the M1 and M2 phenotypes only represent two extreme polarization states of microglia after activation. Because the process of microglia in vivo is much more complex than in vitro, it may include a series of different phenotypes with functional overlap. Various drugs that regulate microglia, including immune modulators, targeting phenotypic transformation, and the interactions between microglia and other nerve cells, are rethinking the therapeutic direction of ICH [7].

2. Polarization of microglia

Microglia are derived from circulating monocytes or precursor cells, blood monocytes, mesodermal progenitor cells, meningeal macrophages, and so on. Microglia are macrophages of the central nervous system, which are in a resting state under physiological conditions and play a "immune monitoring and defense" role in the microenvironment of nerve cells. Microglia are immune cells that specifically exist in the central nervous system. Activated microglia can transform into two phenotypes, M1 or M2, at different stages of disease. This dynamic process of change is called polarization [8]. M1 type microglia have cytotoxic effects and can cause tissue inflammatory damage, which can be caused by interferon γ, Lipopolysaccharide, tumor necrosis factor α M2 type microglia have neuroprotective effects and can promote tissue repair and regeneration.

According to the different stimuli, M2 type can be divided into three subtypes: M2a, M2b, and M2c. During acute brain injury, microglia can dynamically and instantaneously change their phenotype, and activated microglia can mediate neural tissue injury and repair during the course of spinal cord injury, ischemic stroke, and craniocerebral trauma [9]. However, this classification method helps us understand the role of microglia in central nervous system injury, and also provides new therapeutic strategies for it.

3. Interaction between glial cells and other nerve cells

3.1. Astrocytes

Astrocytes can secrete a variety of chemokines that regulate the activation and polarization of microglia, including CXC chemokine ligand 1(CXCL1), CXCL2, CC chemokine ligand 20 (Cc 20), CCR1 and CCR2. In the ICH mouse model induced by collagenase iv, inhibiting the expression of CCL2 or CCR2 can regulate the activation of microglia and down-regulate the expression of i NOS, thus promoting hematoma absorption and improving neurological function [10]. At the same time, the earlier mi R-124 is used after cerebral ischemia, the more the number of M2 microglia macrophages, and the higher the survival rate of nerve cells. Therefore, mi R-124 can also be used as a target for the treatment of microglia activation and other related diseases, including ischemic cerebrovascular disease. At the same time, the inflammatory reaction caused by cerebral ischemia has been alleviated, and the volume of cerebral infarction has also been significantly reduced, suggesting that it is a feasible strategy to treat ischemic cerebrovascular disease by inhibiting the M1 phenotype expression of microglia and up-regulating the M2 phenotype expression. Therefore, it is helpful to understand the pathophysiological mechanism of ICH by studying the polarization and phagocytosis of microglia and other functions of astrocytes.

3.2. Oligodendrocyte

The proliferation and differentiation of oligodendrocyte precursors and mature oligodendrocytes in the white matter surrounding the hematoma can be seen in the ICH mouse model induced by type IV collagenase within 2 weeks of onset, but the specific mechanism is still unclear. In addition, PPAR- γ Agonists can effectively promote the polarization of the M2 phenotype of microglia after cerebral ischemia, indicating PPAR- γ Relevant signal pathways may play an important role in the polarization of M2 type microglia. The peroxynitrite produced by M1 type microglia in the immune response externalizes the phosphoserine residues outside the nerve cells and sends out phagocytic signals, thereby enabling microglia to play a role in brain phagocytosis, causing nerve cell damage. Microglia can undergo M1 type polarization, which plays a neurotoxic role in promoting inflammation, oxidative stress, destroying the blood brain barrier, and inhibiting nerve regeneration. The significant decrease in M1 phenotypic markers and the significant increase in M2 phenotypic markers suggest that blocking the mTORC1 signaling pathway can regulate microglia and transform the damaging M1 phenotype into a protective M2 phenotype. Animal experiments have shown that after ultrasound guided whole blood injection to induce ICH, oligodendrocytes can secrete haptoglobin and exert a neuroprotective effect within 24 hours against the toxic effects of heme chloride and iron ions produced after hemoglobin lysis.

4. Microglial cell polarization and ischemic cerebrovascular disease

4.1. The role of microglial cell polarization in ischemic cerebrovascular disease

Activation of microglia is a complex process involving multiple factors and channels, which can produce different polarization phenotypes under different pathophysiological conditions, thereby playing a "double edged sword" role. Aggregation and activation of microglia were observed around the injured axon. Activated microglia can produce a large number of inflammatory factors, causing "secondary injury" of neurons, leading to neuronal apoptosis. Polarization of microglia into M1 type can induce the production of various inflammatory factors, and changes in inflammatory factors at the molecular level can reflect changes in the biological functions of microglia after ICH.

Immunohistochemical staining or flow cytometry analysis of brain tissue from patients with ICH can identify surface markers of microglia. Western blot analysis showed that the expression of CD206, a specific marker of M2 type microglia, increased in the ICH 24 h group, and gradually increased with the increase of ICH time in the ICH 72 h group. Compared with the ICH group at the same time point, the expression of CD206 was further increased in both the ICH 24 h group and the ICH 72 h group, as shown in Figure 1.

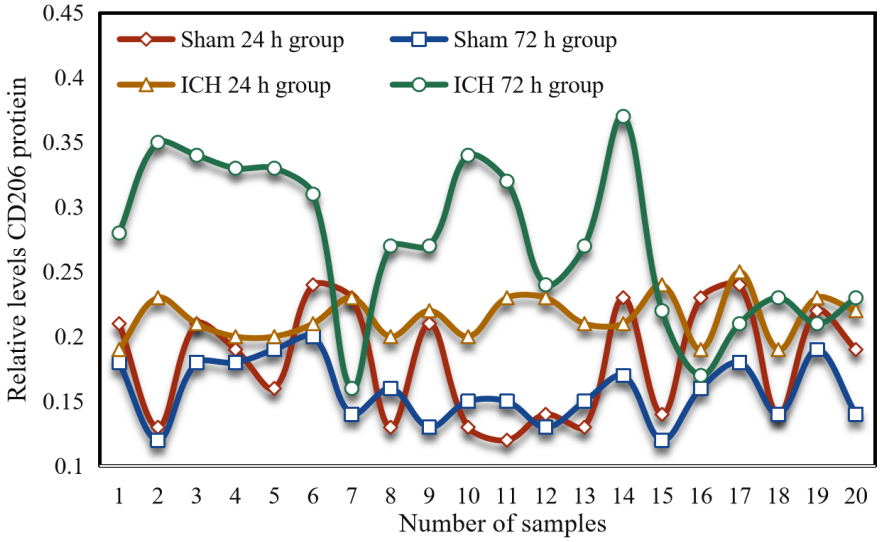

Figure 1: Expression of M2 type microglia in each group

M1 type microglia can secrete a variety of proinflammatory and chemotactic factors, causing neuroinflammatory reactions and inducing neuronal apoptosis. M2 type microglia mainly engulf and clear pathogens, repair tissue cells. The conditioned medium of M1 type microglia can aggravate the death of neural cells under OGD conditions, while the conditioned medium of M2 type microglia can protect neural cells and resist the damage caused by OGD, suggesting that different phenotypes of microglia can play different regulatory roles on the death of neural cells after cerebral ischemia.

4.2. Establishment of Intracerebral Hemorr-Hage animal model

The regulatory mechanism of M1 type microglia polarization in ischemic cerebrovascular disease: After cerebral ischemia, M1 type microglia mainly exert damage through two pathways. After ICH, there was a significant change in the expression of inflammatory factors induced by M1 type microglia. The observation of ICH rat models induced by type IV collagenase and autologous blood showed that the serum IL-1 β、 Inflammatory factors such as IL-6, TNF, and inducible nitric oxide synthase mRNA increase during the acute phase, and the corresponding protein expression changes follow similar disease progression nodes. M2 type microglia convert into phagocytes, creating conditions for nerve cell regeneration, survival of nerve cells surrounding dead cells, and formation of new neural structures through phagocytosis of harmful substances such as dead nerve cells, degenerated synapses, and infiltrating neutrophils in the brain. The various expressions of tight junction proteins in the Sham 24 h and Sham 72 h groups were higher than those in the ICH group at the same time point. Compared with the ICH group at the same time point, the expression of Sham 24 h group and Sham 72 h group showed an increasing trend, but the difference was not statistically significant.

As a pleiotropic cytokine, IL-4 is involved in the regulation of various immune and inflammatory reactions, and one of its anti-inflammatory effects is that it can polarize macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. By the chronic stage of ICH,

the expression of most inflammatory factors has returned to normal level, but it is still difficult to determine whether the above inflammatory factors have changed in the chronic stage of ICH and whether these changes affect the recovery of neurological function.

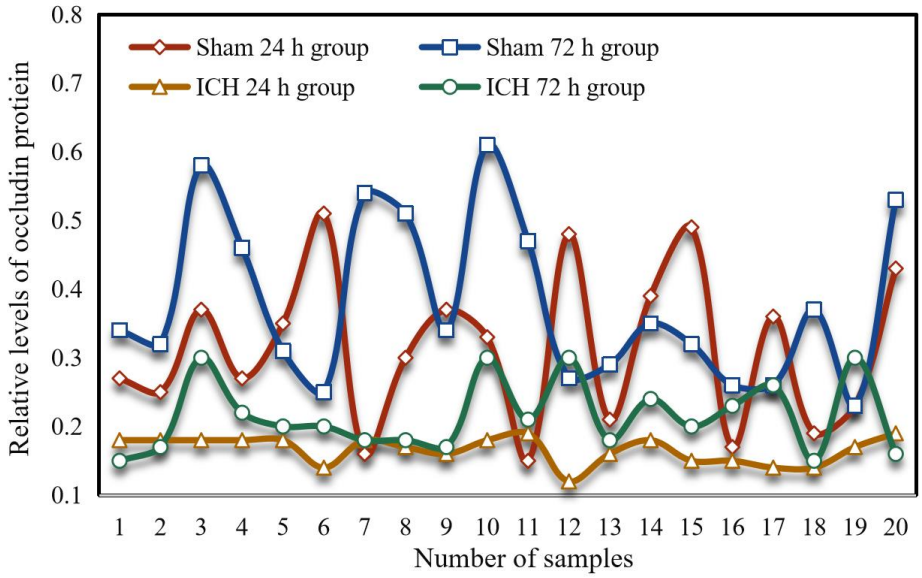

Figure 2: Expression level of tight junction protein in each group

5. Conclusions

Microglia, as the main effector cells of the central nervous system, are the first to perceive changes in the intracellular microenvironment. Phenotypic regulation of microglia involves the regulation of a series of factors and signal pathways. Simply inhibiting the activation of microglia may mask the neuroprotective effect of microglia. This article has taken ICH as an example to conduct research. The peroxynitrite produced by M1 type microglia in the immune reaction externalizes the phosphoserine residues outside the nerve cells and sends out phagocytic signals, thereby enabling microglia to play a role in brain phagocytosis, causing nerve cell damage. The expression of M1 type and M2 type microglia increased, and the main type of microglia was M1 type. In addition, the expression of M1 type microglia in the ICH 72 h group decreased compared to the ICH 24 h group, while the expression of M2 type microglia in the ICH 72 h group increased compared to the ICH 24 h group. Compared with Sham group, the increased expression trend of M1 type microglia after ICH was similar to that of TLR4/NF- κ the increasing trend of B is consistent. Although some in vitro studies have shown that the polarization process of human microglia may be consistent with that of rodents, this does not mean that the polarization mechanism of rodent microglia will be fully applicable to humans. Therefore, the use of microglial phenotypic polarization for the treatment of ischemic cerebrovascular diseases still requires further research.

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