ISSN: 2641-1911
DOI: 10.33552/ANN.2020.07.000675
Archives in Neurology & Neuroscience
Iris Publishers

Mini Review

Discrepancy of Microglia Activation in Acute Ischemic Stroke and Chronic Cerebral Hypoperfusion

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Received Date: May 15, 2020

Published Date: May 26, 2020

Abstracts

Acute ischemic stroke and chronic cerebral hypoperfusion share some common pathological changes and mechanisms. Inflammation plays an important rolein both acute and chronic cerebral ischemia.Microglia represent the immune system of the mammalian brain and are critically involved in cerebral ischemia, whichis an exciting target for future therapies. A major challenge for clinical translation will be the insufficient understanding of microglial heterogeneity. Microglia display diverse and brain region-specific phenotypes, and itsactivation occurs as a graded response in vivo. Through this mini review, webrieflysummarize the current knowledge about the discrepancy of temporal, spatial, morphological and functional changes of microglia in the brain under the condition of acute ischemic stroke and chroniccerebral ischemia, to provide some new clues for developing different strategies against neuroinflammatory injury resulting from acute and chronic cerebral ischemia.

Mini Review

Acute ischemic stroke and chronic cerebral hypoperfusion share some common pathological changes including white matter injury and cognitive dysfunction. Currently, there is no effective therapy for chronic cerebral hypoperfusion-induced subcortical vascular dementia, and the only approved therapy for stroke patients is to achieve reperfusionvia clot removal. Inflammation plays an important role in both acute and chronic cerebral ischemia. Microglia is the major endogenous effector in the innate immunity of the brain, constitute approximately 5–10% of adult brain cells, and display diverse and brain region-specific phenotypes. Microglia are essential to maintain cell homeostasis in the healthy brain, and rapidly activate and undergo proliferation, migration, and phagocytosis when the brain suffers ischemic injury, then mediates critical degenerative and regenerative responses, which is an exciting target for future therapies. In this mini review, webriefly summarize the current knowledge about the discrepancy of microglia activation in the brain under the condition of acute ischemic stroke and chronic cerebral ischemia, to provide some new clues for developing different strategies against acute and chronic cerebral ischemia.

Acute and chronic cerebral ischemia induce different changes in microglia morphology. ‘‘Resting microglia’’ exhibit a ramified morphology characterized by a small soma and fine processes under normal circumstances to perform immunological surveillance. Microglial activation experienced morphological changes like cell body hypertrophy and process thickening, with coinciding upregulation of a variety of cell surface markers. Inacute ischemic stroke, microglia were both hyper- and de-ramified in striatal and cortical regions after 60 min of focal cerebral ischemia. However, a de-ramified morphology was prominent when reperfusion was performed, and process activity was severely blunted proximal to the necrotic core after ischemic stroke and 24h of reperfusion. CD11b expression, but not iNOS expression, was increased in regions of hyper- and de-ramified microglia during the course of

ischemic stroke and 24 h of reperfusion [1,2]. However, microglia activation requires some residual capillary blood flow, complete perfusion loss as during bilateral common carotid artery occlusion (BCCAO), a chronic cerebral hypoperfusionmodel did not support microglial de-ramification [2]. In addition, the robust de-ramification and amoeboid-like morphology of a portion of Iba-1 positive cells most proximal to the necrotic core, which could not detected in the model of chronic cerebral hypoperfusion. Except for blood flow, the corresponding molecular level changes supporting the morphological change following acute and chronic cerebral ischemia have not been studied.

Besides structural changes, microgliaundergo proliferation and phenotype changes after acute and chronic cerebral ischemia. It is clear from extensive studies that microglia proliferate in response to prolonged cerebral ischemia [3], in spite of the existence of a microglia progenitor cell [4] or proliferation of residual microglia [5] is an ongoing controversy. The reactive microglia can be subdivided into a pro-inflammatory state (M1) releasing reactive oxygen species, cytokines and proteases, which exacerbate neuronal injury or anti-inflammatory state (M2) supporting regeneration. Polarisation of microglia is a dynamic, context-specific process, with temporal integration determining the neuroinflammatory changes seen in the acute versus the chronic setting. In the acute cerebral ischemiamodelof permanent middle cerebral artery occlusion (pMCAO), it were observed that M2-type microglia/macrophage marker CD206 increased from 6h after ischemia, while CD68 and Ym1 increased from 24h after ischemia, which lasted to the 7th day [6]. In the transient middle cerebral artery occlusion (tMCAO) model, the mRNA expression of M2 microglia/macrophage markers, including CD206, Arg1, TGF, Ym1/2, IL-10 and CCL22 began to increase at day 1-3 after reperfusion, peaked at day 3-5, decreased at day 5-7, and almost returned to normal level at day 14. Meanwhile the mRNA expression of M1 markers including iNOS, CD11b, CD16, CD32, and CD86 were gradually increased from day 3 and remained elevated for at least 14 days after ischemia [7]. The above results suggested that the microglia in early stage of acute ischemic stroke were mainly M2-type and gradually transformed into M1-type. Apart from temporal changes, the spatialchanges was also detected in acute cerebral ischemia, it was found that the polarization degree of microglia after ischemia is related to the ischemic site, which is more significant in cortex, and the difference increased with the aggravation of reperfusion injury [1]. BCCAO or bilateral common carotid artery stenosis (BCAS) method are usually used to create the chronic cerebral ischemia model. From 1 week to 9 weeks after ischemia, the number of Iba-1 positive cells in the cortex, hippocampus, corpus callosum and striatum were all increased [8-10]. Along with the proliferation of microglia, M1 microglial cells markers iNOS, CD86 and CD16 expression increased, with the expression of M2 marker Arg1 reduced, suggesting that microglia were mainly transformed into M1-type after chronic ischemia [11-13], which is different from acute cerebral ischemia.

This M1/M2 nomenclature does not fully account for the microglial heterogeneity, since some simultaneous expression of both M1/M2 markers at the single-cell level. Recently, a protocol for the rapid isolation of microglia from different brain regions in a single adult mouse brain hemisphere were provided, and how to use these sorted microglia for plate-based deep single-cell RNA sequencing was demonstrated [14]. Further dissection of such heterogeneity can be achieved through efficient isolation of microglia from a given region of interest. With the advance of single-cell genomic approaches, the heterogeneity of microgliawas revealed [15,16], further contributing to our understanding of microglia heterogeneity in relation to age, sex, and CNS disease. The single-cell genomic approachescould also help us to comprehend the corresponding molecular level changes supporting the morphological and functional changes following acute and chronic cerebral ischemia.

Age-dependent alterations in microglia behavior have been implicated in cerebral ischemia. It was found during stroke recovery by comparing the transcriptional profiles of young versus aged microglia that in young microglia are indicative of up regulation in cell movement, cell interactions, inflammatory responses and angiogenesis, while aged microglia exhibited a reduction or no change in these features [17], which sheds light on new potential strategies to improve microglial functions in aged stroke victims.However, the age-dependent alterations in microglia behavior in the chronic cerebral ischemia is unknown. It has been showed that aged WT mice exhibited white matter and hippocampal damage and an increase in the number of microglia in the brain; these characteristics were not seen in transient receptor potential melastatin 2 (TRPM2)-KO mice, suggesting that TRPM2 plays a critical role in exacerbating inflammation and cognitive dysfunction during aging in chronic cerebral hypoperfusion [18]. However, whether TRPM2 plays a critical role in the age-dependent alterations in microglia behavior in the stroke is unclear.

Currently, there are no clinically-approved medicines targeting inflammation post-ischaemia. A major developmental challenge for clinical translation will be the selective suppression of the harmful effects of microglial activation after cerebral ischemia whilst retaining or enhancing the regenerative responses of microglia. Identifying different key molecular and cellular mediators of microgliaproliferationor polarization for acute and chronic cerebral ischemia will provide critical information needed to develop novel therapies.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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