Biomedicine & Pharmacotherapy 105 (2018) 518–525

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Treatment targets for M2 microglia polarization in ischemic stroke

Ji wang[a,1], Hongyi xing[a,1], Lin wan[b,2], Xingjun jiang[a,3], Chen wang[a,4], Yan wu[a,*,5]

[a] Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
[b] The Children's Hospital of Soochow, Jiangsu, Hematology and Oncology, China

ARTICLE INFO

Keywords:
Microglia
M2 polarization
Ischemic stroke
Inflammation
Neuroprotection

ABSTRACT

As the first line of defense in the nervous system, resident microglia are the predominant immune cells in the brain. In diseases of the central nervous system such as stroke, Alzheimer's disease, and Parkinson's disease, they often cause inflammation or phagocytosis; however, some studies have found that despite the current controversy over M1, M2 polarization could be beneficial. Ischemic stroke is the third most common cause of death in humans. Patients who survive an ischemic stroke might experience a clear decline in their quality of life, owing to conditions such as hemiplegic paralysis and aphasia. After stroke, the activated microglia become a double-edged sword, with distinct phenotypic changes to the deleterious M1 and neuroprotective M2 types. Therefore, methods for promoting the differentiation of microglia into the M2 polarized form to alleviate harmful reactions after stroke have become a topic of interest in recent years. Subsequently, the discovery of new drugs related to M2 polarization has enabled the realization of targeted therapies. In the present review, we discussed the neuroprotective effects of microglia M2 polarization and the potential mechanisms and drugs by which microglia can be transformed into the M2 polarized type after stroke.

1. Introduction

Stroke is the third most common cause of human death in modern society. Recently, it was found that the inflammatory and immune reactions that occur after stroke can aggravate cellular damage. This inflammation, which is a form of sterility, has been shown to be activated at each stage of stroke from the early destructive events to the late stages of brain tissue repair and vascular regeneration [1–3]. In further studies on these findings, both animal experiments and postmortem examinations of patients after stroke strongly demonstrated the significant effect of inflammation during the later stages of stroke [4–8]. Therefore, the intervention of microglia after stroke might be a therapeutic target.

Microglia were first discovered by Pío del Río Hortega (1882–1945). Hortega cells were described as small cells with short ramifications and, subsequently, researchers named them microglia [9–11]. There is an increasing body of evidence to suggest that microglia in the adult brain are derived from primitive myeloid progenitors in the yolk sac very early in embryonic development [12]. Thus, they are referred to as the resident immune cells of the brain. A series of studies have demonstrated the inflammatory response of microglia on various stages in the development of many diseases of the nervous system, including stroke, Parkinson's disease, and Alzheimer's disease [13–18]. In the absence of cellular stress, microglia participate in synaptic development and pruning. The need to investigate this important immune cell has led to the development of novel experimental technologies. Presently, techniques for studying microglia include two-photon excitation time-lapse microscopy, organotypic slice cultures, serial block-face scanning electron microscopy, and animal behavior [19].

Because the actions of microglia are similar to those of peripheral

Abbreviations: PACAP, pituitary adenylate cyclase–activating polypeptide; OGA, beta-*N*-acetylglucosaminidase; FAM19A3, TAFA3, TAFA family (TAFA1-5); TPA, tissue plasminogen activator; GSH, glutathione-SH; NGF, nerve growth factor; BCL-2/BCL-X1, B cell leukemia/lymphoma 2; YM1/2, chitinase-3 like protein; ARG-1, arginase I; IGF-1, insulin-like growth factor-1; FIZZI, found in inflammatory zone 1; HO-1, heme oxygenase-1; CD206, mannose receptor; CREB, cAMP response element-binding protein; NF-kB, nuclear factor-κB; HV1, voltage-gated proton channel; ASK1, apoptosis signal-regulating kinase 1; VIP, vasoactive intestinal peptide; iNOS, inducible nitric oxide synthase; TLR4, toll-like receptor 4; ROS, reactive oxygen species; 5-LO, 5-Lipoxygenase; Iba-1, ionized calcium-binding receptor adapter molecular 1; CXCL1, the chemokine ligand 1; MCP-1, monocyte chemoattractant protein-1; AMPK, AMP-activated protein kinase; Nrf2, nuclear factor erythroid 2-related factor 2; ST2, a member of the interleukin (IL) 1 receptor family

* Corresponding author.
E-mail address: wuyan_whunion@163.com (Y. wu).
[1] The common first author.
[2] The second author.
[3] The third author.
[4] The forth author.
[5] Denotes Corresponding author.

https://doi.org/10.1016/j.biopha.2018.05.143
Received 31 March 2018; Received in revised form 25 May 2018; Accepted 28 May 2018

macrophages, present studies have divided microglia into a classical pro-inflammatory state (M1) and an alternative anti-inflammatory state (M2) [20–22]. Despite the adoption of a similar classification system, many differences have been found between microglia and peripheral macrophages. Therefore, some studies have stated that this polarization remains controversial and highlight the need to distinguish microglia based on transcriptomic and proteomic profiling considering their stimulus and disease specificity [23,24]. We have used these theories to analyze our perspective. Several studies have also suggested that microglia could be in static or active states. This controversy required almost 2 years of research to determine that microglia do not have a so-called resting state but are still involved in intracranial sentinel function [25,26]. Moreover, several studies have shown that the M2 population was neuroprotective after stroke [2,27–29]. The protective effect of the M2 phenotype is mediated predominantly via the ability to engulf debris and promote the repair and regeneration of brain tissue after cerebral ischemia. In addition, the inflammatory factors of the M1 phenotype aggravate post-stroke symptoms. Therefore, the response of microglia after stroke is an important prognostic factor [27].

2. Current knowledge on M2 polarized microglia

2.1. Cell surface markers

Microglia are involved in tissue repair, debris removal, and the maintenance of normal tissue dynamics after infection or injury, especially in the M2 polarized state. The resident microglia are M2 polarized during the early stages of stroke; however, they are transformed into the M1 polarized state in the ischemic penumbra region [27]. Therefore, it is important to distinguish the cell markers and characteristics of the cell type based on the neuroprotective function of M2 polarization. If we could precisely mark the microglia, then we could preserve the M2 phenotype and alleviate those destroyed by inflammatory factors.

Primary microglia have been treated with inflammatory factors such as lipopolysaccharide (LPS) and interferon (IFN)-γ in vitro and M1 polarization has been characterized based on the upregulation of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-2, IFN-γ, C-X-C motif chemokine ligand 9 (CXCL9), CXCL10, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) [30]. Notably, the same study reported that a transition state of microglia was found at the point of transition, which some researchers considered to be another therapeutic target [31]. Furthermore, under oxygen-deprived conditions arising from middle cerebral artery occlusion (MCAO), the presence of mixed types of microglia in the animal model showed that it did not induce fixation similar to that observed in vitro. These results indicated that the microglial cell types were in a dynamic state and it might be possible to artificially control these changes. These results comprehensively demonstrated the feasibility of this therapeutic target. To understand the functional changes in microglia after stroke, we summarized some typical comprehensive details of the microglia and M2 markers, which are presented in Table 1. Notably, this table is not entirely complete because the polarization of microglia embodies a complex and overlapping state.

Studies have found that the expression of type M2 polarization receptors and cytokine IL-4 secretion decreased with age [31,63]. Age-related inflammatory status is related to the type of microglia expressed, which appears to be related to different time points after stroke. Other research studies have found that IL-4 is essential for microglial cell phenotype expression and gradual recovery after an ischemic stroke [64]. Combined with the above results, we inferred that IL-4 might be involved in microglial typing and the potential improvement of post-stroke symptoms.

2.2. Morphology of M2 microglia phenotype after stroke

2.2.1. Changes in morphology

Microglia, first found by Robertson in 1899 using a platinum stain, are the third class of cells, in addition to neurons and astrocytes, which are characterized by a variety of small somas [65]. After the activation of microglia, a series of morphological changes occur, producing ramified, primed, reactive, and amoeboid morphologies [66]. Some findings have demonstrated that microglia in the sub-ventricular zone and injured striatum have different activity and morphology after stroke [67]. In the mouse model of permanent MCAO, the activated microglia were mainly concentrated in the lesion edge. The microglia transformed into an amoeboid shape during the motion of the ischemic core [68]. Using more intuitive methods, the photomicrographs in Fig. 1 illustrate three different phenotypes (A, ramified; B, intermediate; and C, amoeboid), which are particularly distinctive [69].

2.2.2. Changes in cell function accompanying morphological changes

Morphological transformations in microglia are associated with changes in their functions such as phagocytosis and cytokine transformation [70]. One study showed that to deal with these lesions in a healthy brain, microglia are immediately activated and proceed to change in size, pro-inflammatory protein production, and functions such as proliferation, migration, and phagocytosis [71].

Microglia are the guardians of the brain and are highly reactive in their resting state. Many research studies have shown that in the “resting” state, microglia are involved in synaptic loop formation, synaptic pruning, and monitoring of brain changes when the brain is in an unstressed state [25,26] (Fig. 2). In one study with reduced or absent purinergic P2Y12 receptor (P2Y12) expression, which relate to microglial activation and migration, $Iba1^+$ microglia were a circular amoeboid shape [72]. In addition, colony-stimulating factor-1 excreted by adipose-tissue-derived mesenchymal stem cells (ASCs) might alter the cell morphology and upregulate the expression of type M2 molecules in conditioned medium by the activation of phosphoinositide-3-kinase/Akt (PI3K/Akt) [73]. These observations might indicate that the morphological changes are associated with receptor functions and the complex secretion ability of cells, which may indeed be the initiating factors.

3. Contact of neurons, astrocytes, and endothelial cells with M2 phenotype after stroke

3.1. Neurons

After pathological changes, the microglia receive “distress” signals from nearby neurons, which initiate rescue processes by effective phagocytosis that target harmful substances or hazardous debris in the inflammatory environment, such as fractalkine (FKN) and IL-34 [74]. Internally, fractalkine (cx3cl1/cx3cr1) not only acts as a link between neurons and microglia, but also participates in the secretion of IL-1β by microglia after transient MCAO [17]. The release of IL-4 by neurons promotes the induction of microglia to the M2 phenotype and the regeneration of necrotic tissue. Previous studies have suggested that the promotion of IL-4 secretion by neurons or treatment with IL-4 alone might be a promising strategy for stroke treatment [75,76].

In other studies, for example in Alzheimer’s disease inflammation, CX3CR1 knockout (fractalkine receptor) protected against neuronal loss and neurons could be damaged by the secretion of inflammatory factors by microglia [13,14]. In contrast, the secretion of clusterin by astrocytes directly activates microglia [13,14]. It has been documented that neurons and microglia are linked by CD200-CD200R signaling, which is a transmembrane glycoprotein that exists on neurons and mediates the anti-inflammatory effect [63]. Thus, these findings provide ample evidence that the intercellular communication is more abundant than previously believed.