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Review Article

The Role of Infiltrating Monocytes/Macrophages in Intracerebral Hemorrhage

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Abstract

Intra Cerebral Hemorrhage (ICH), a subtype of stroke, pose a serious threat to human life. Recent studies have shown that neuroinflammation is deeply related to the progression of ICH-induced brain injury. After the onset of ICH, peripheral circulatory system monocytes/macrophages can be activated within hours and recruited to the peri-hematoma regions. Traditionally, activation of monocytes/macrophages is considered to play a deleterious role in cerebral hemorrhage, as inhibition of their activation attenuates hemorrhage-induced brain injury. However, increasing evidence shows that activation of monocytes/macrophages is critical for hematoma clearance and functional recovery after ICH. Therefore, a better understanding of the mechanisms underlying their functional changes following ICH is necessary. We briefly review the activation, function, and phenotypes of monocytes/macrophages after ICH and then suggest additional therapies targeting monocytes/macrophages that may be aim at not only suppressing their activation, but also modulating them at different stages of ICH. However, more work is needed to elucidate the cellular and molecular mechanisms of infiltrating monocyte differentiation and macrophage polarization in a hemorrhagic brain environment.

Keywords: Intracerebral hemorrhage; Monocytes; Macrophages; Polarization

Introduction

Intra Cerebral Hemorrhage (ICH) is a devastating stroke subtype affecting nearly 2 million patients all over the word every year. While the initial neurological deficit is caused by the mass effect of the hemorrhage itself, there is increasing recognition that an inflammatory process contributes to further injury over the ensuing days [1-3]. After ICH, extravasation of plasma protein and cellular elements from the blood vessels into the brain tissue represents the triggering factor for the mobilization and activation of the brain immune cells. As a result, microglia, astrocytes and endothelium cells secrete inflammatory cytokines and chemokines, which induce robust recruitment of leukocytes from blood into the peri-hematoma region within hours to a few days, such as monocytes/macrophages, neutrophils and lymphocytes.

Among these circulating immune cells, monocytes/macrophages have been shown to play a particularly important role. Initially, the presence of monocytes/macrophages at the injury region was considered as a marker of an exacerbated inflammatory response that contributed to brain injury. However, recent studies show that infiltrating monocytes/macrophages in the brain post-ICH contribute to functional recovery, implying a protective effect of these cells after ICH [4-6]. These reports suggest a more complex and multiphase role of infiltrating monocytes/macrophages, suggesting a potential direction for ICH therapies.

Activation of monocytes/macrophages in ICH

Monocytes constitute a heterogeneous group of cells, including an inflammatory subset and patrolling subset. The inflammatory monocytes are specifically recruited to an injury site and differentiated into macrophages. The patrolling subsets are recruited to normal tissue and participate in host defense and repair after injury. After tissue injury, early inflammatory monocytes and late patrolling monocytes are sequentially recruited to the lesion in a controlled manner for inflammation and repair/healing [7].

Following ICH, the inflammatory monocytes migrate into and around the lesion site as soon as possible and then differentiate into potent phagocytic cells, macrophages, in the hemorrhagic brain. Actually, inflammatory monocytes differentiate into macrophages in the hemorrhagic brain as early as 12 hours after ICH and can be seen for a long time in the brain, even months [8]. It is reported that inflammatory monocytes are the most numerous blood-derived leukocytes in the brain at day 3 after experimental ICH [9]. In recent hemorrhages (within 5-10 days after stroke), a large number of the macrophage system cells around the hemorrhage core originate from the blood flow by activation of circulating monocytes, while a lesser number result from local microglia activation [10].

After ICH, the migration of monocytes/macrophages is correlated to many factors, such as neutrophils and inflammation-induced high expression of chemokine and chemokine receptors. It has been reported that up-regulation of Monocyte Chemo attractant Protein-1(MCP-1) and its receptor CC chemokine Receptor 2 (CCR2) could induce greater accumulation of monocytes/macrophages and exacerbate inflammatory injury in the hemorrhagic brain [11]. However, there is a relative paucity of in vivo studies related to the activity of patrolling monocytes following ICH.

Function of monocytes/macrophages in ICH

In a rat model of ICH, robust blood-derived inflammatory

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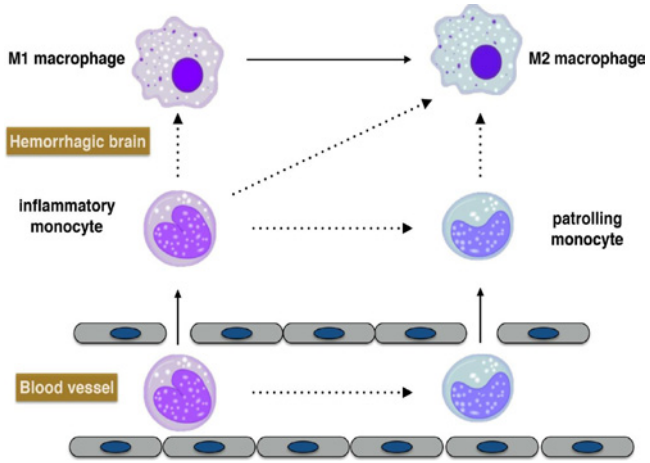

Figure 1: Potential lineage relationships of monocytes and macrophages after ICH. In steady-state, monocyte conversion from inflammatory subset to patrolling subset may occur in blood and bone marrow [27]. It is generally accepted that inflammatory monocytes give rise to M1 macrophages in tissue. Other lineage relationships, indicated by dashed arrows, remain to be experimentally explored in the condition of intracerebral hemorrhage.

monocytes are recruited to the region surrounding the hematoma and contribute to early motor deficits [8]. Besides, a higher serum CCL2 level, the dominant chemokine for monocyte recruitment, at 24 h is also associated with worse early functional outcomes in patients with ICH [9]. Lee et al. showed that a splenectomy 3 days prior to ICH rescued brain edema and infiltrating macrophages and neutrophils [10,11], further implicating the role of peripheral macrophages in ICH damage [12]. In addition, the peripheral monocyte count is also associated with 30-day case-fatality in ICH patients [13,14]. These studies suggest that peripheral monocytes/macrophages migrate to the hematoma region and then lead to progressive brain damage, and inhibition of their trafficking into the brain or a reduction in the peripheral monocytes/macrophages may have a therapeutic benefit in ICH.

However, studies have also proven that monocytes/macrophages infiltrating brain parenchyma after ICH may play a beneficial role in clearance of the hematoma, anti-inflammation and repair as well as promote recovery from ICH injury [4,5]. Zhao et al. reported that macrophages play a key role in promoting hematoma absorption and protecting other brain cells from ICH-induced injury via PPARγ [15]. After hemorrhage, M2 macrophage are expected to increase over time as the peri-hematoma milieu transitions into an immune dampened tissue repair phage in which M2 macrophage play a pivotal role [16]. Besides, it's also proved that CD163, mainly localized on the surface of monocytes/macrophages, counteract the inflammation and promote hematoma absorption as well as improves neurological functions in patients with intra cerebral hemorrhage [17,18]. Recently, in peripheral monocyte/macrophage-depleted mice, ICH was shown to induce a larger brain lesion volume and a more severe neurological deficit than those in control mice at day 3 post-ICH, suggesting a protective role of monocytes/macrophages in ICH [5].

Considering these evolutionarily adaptive functions, we believe that infiltrating monocytes/macrophages play a critical role in the innate immune response after ICH. On the one hand, they play a deleterious role via releasing a variety of inflammatory cytokines and toxic substances. On the other hand, they could also be beneficial through clearance of hematoma and repair. Therefore, a better understanding of the mechanisms underlying the functional changes of monocytes/macrophages in the pathobiology of ICH is essential to develop successful immune interventions. Maybe different phenotypes of monocytes/macrophages could account for their biphasic roles under different pathological conditions.

Phenotypes of monocytes/macrophages in ICH

It is widely accepted that there are two types of macrophages: classically activated macrophages (M1) and alternatively activated macrophages (M2). M1 cells express high levels of CD86, CD16, CD32 and MHCII on their surface and produce large amounts of pro-inflammatory cytokines, such as TNF-α, IL-6, iNOS and NO, exacerbating tissue damage. M2 cells have low levels of MHCII and CD86 and poorly stimulate or even inhibit T cell proliferation but express a number of protein important for pinocytosis of carbohydrate-rich parasitic products and promote tissue repair [19]. It is well known that macrophages display plasticity in their characteristics and can change phenotype and function depending on the microenvironment.

It is accepted that M2 macrophages co-exist with M1 macrophages throughout the course of disease development, although M2 cells are not the predominant macrophage phenotype at the initial phase. There is a gradual increase in the population of M2 cells during the process of inflammation until the peak of disease, whereas the M1 cell population is relatively reduced in the later phases of disease development [20]. An increase in the M2 cell population in the peak and later stages of disease may contribute to a decrease in inflammation by expressing anti-inflammatory cytokines. Thus, the balance between macrophage phenotypes is important in disease development, and a disorder of balance may be either detrimental or beneficial to disease progress. Breakthrough research on macrophages has revealed several transcriptional regulators that serve as central switches to turn on a group of M1 or M2 genes and achieve polarization. The most studied are the IRF/STAT, JNK and Akt/PI3 signaling pathways [21,22]. In the recent years, different studies note that certain miRNAs are also involved in the acquisition of the M1 and M2macrophageactivated states, such as miRNA155 and miRNA124 [19,23]. In addition, the existence of other cells may also affect the phenotype of macrophages, such as glia and neural stem cells [5,24].

In ICH, the microenvironment greatly influences the phenotypic changes in macrophages, resulting in different gene expression patterns and bio functions in the same brain tissue. Currently, there is a general lack of information about the time course of M1 and M2 macrophage activation. Yang et al. found that M2 markers (Arg 1, IL-13, YM 1, and CD206) increased within 1 day, but the M1 markers (IL-1β, TNF-α, and IL-6)increased as early as 3 h after ICH [25]. They also showed that early injection of IL-4 could promote anti-inflammation, which favors repair via inhibiting M1 cell activation while enhancing M2 cell activation after experimental ICH. This suggests that drugs with the ability to promote the shift to the M2 phenotype might be beneficial for the treatment of ICH. In addition, other peripheral immune cells may also affect macrophage phenotypes after ICH. For instance, it has been shown that regulatory T cells can induce

macrophages towards M2 polarization through the IL-10/GSK3β / PTEN axis [26].

Circulating monocytes possess 3 major distinct phenotypes in human and mice based on the expression of specific surface markers. The phenotype(CD14+CD16- in humans and Ly6ChiCD43- in mice) expressing a high level of CCR2 is the classical monocytes, which can migrate to the site of injury and infection where they differentiate into macrophages; the phenotype (CD14dimCD16+ in humans and Ly6CloCD43+ in mice) expressing a high level of CX3CR1 is the non classical patrolling monocytes, which exhibit a unique ability to patrol the resting vasculature and remove debris; a third phenotype (CD14+CD16+ in humans and Ly6ChiCD43+ in mice) with high expression of CX3CR1 is the intermediate monocytes, which also generally possess inflammatory characteristics [27]. It has been reported that the Ly6Clomonocytes recruited during inflammation only differentiate into M2 macrophages, while Ly6Chimonocytespolarize to M1 macrophages in the early phase of inflammation but polarized to M2 macrophages in the later phage when the inflammation was receding in renal tubulointerstitial injury [28,29]. It has also been reported that PPARγ activation primes monocyte differentiation into M2 macrophages in human atherosclerotic lesions [30]. However, the exact contribution of different monocyte phenotypes in ICH is still elusive as studies related to monocyte differentiation and its influential factors following ICH are limited (Figure 1).

Monocytes/macrophages as a potential candidate for cell-based therapy for ICH

As infiltrating monocytes/macrophages play a key role in the neuroinflammation induced by ICH, strategies inhibiting inflammatory monocyte infiltration and transformation into M1 macrophages would likely be effective in controlling injury and improving brain recovery following ICH. It has been proven that neutrophil depletion or TLR4 deficiency prior to ICH leads to the infiltration of fewer monocytes into the peri-hematoma brain and improves the functional outcome [31,32]. Strategies that aim to reduce the level of chemokine and chemokine receptors also be beneficial following ICH but need to be studied further.

In addition, the M1 phenotype damage and M2 phenotype repair give us a promising therapeutic method for regulating macrophage polarization in ICH treatment. Promoting the molecular signaling switch that leads to M2 activation or inhibiting M1 activation may be another approach to treat ICH. It has been shown that soluble factors released from glial cells or neural stem cells polarize macrophages to the M2 phenotype [5,24]. Besides, Zhao et al. showed that minocycline, a selective inhibitor of M1 phenotype, attenuated iron accumulation and early neuronal death after ICH in experimental rats [33].

Conclusion and Future Prospects

Monocytes/macrophages are among the most potent modulators of pathological changes in the brain after ICH; however, these cells are apparently double-edged swords in the battle for disease development. Exclusively suppressing monocyte/macrophage migration and activation might compromise the protective effects of monocytes/macrophages and is therefore not a suitable therapeutic strategy for hemorrhagic brain injury. There is a need for the establishment of the best strategy to modulate monocytes/macrophages and drive them to a protective phenotype at different stages of ICH.

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