COMMENTARY

Rethinking the Roles of Inflammation in the Intracerebral Hemorrhage

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Blood in the vessels bleeds into the brain parenchyma resulting in the intracerebral hemorrhage (ICH) [1]. The direct mass effect of the rapidly formed hematoma causes the brain damage, which leads to neurologic deficit. Thus, clearing the hematoma may be beneficial to the patient with ICH. However, the Surgical Trial in Intracerebral Hemorrhage (STICH) trial showed no overall benefit from early hematoma evacuation compared to initial conservative treatment [2]. Therefore, the secondary brain injury caused by the metabolic products or the components of hematoma attracted more researchers' attention [3]. Converging evidence shows that both central and peripheral inflammation play critical roles in the ICH-induced secondary brain injury [3-8]. Previously, most studies concentrated on the downstream inflammatory events, such as proinflammatory cytokines, showed that inflammatory responses contribute to the secondary brain injury after ICH, while no direct clinical effects on targeting these downstream events have been achieved [7]. Hence, it is worth thinking about why this kind of therapeutic strategies has no direct clinical effects and rethinking the roles of inflammation in the ICH.

Central Inflammation Contributes to Secondary Brain Injury After ICH

Once ICH occurs, the hematoma gradually dissociated and released its components, such as hemoglobin (Hb),

☐ Qing-Wu Yang yangqwmlys@hotmail.com heme, iron, etc., into the perihematoma tissues [4, 9–11]. Then, these components of hematoma immediately trigger the inflammatory responses, which subsequently recruit and activate most inflammatory cells involved in the brain inflammatory injury. For example, the activated resident microglia and astrocyte, releasing a large amount of proinflammatory cytokines such as interleukin (IL)-6, TNF- α , and IL-1 β , are in response to the blood components implicated in the initial brain injury after ICH [1, 7]. This inflammatory cascade leads to more neuron death; meanwhile, the dead neurons release the dangerassociated molecular patterns (DAMPs), such as highmobility group protein box-1 (HMGB1) [12], to recruit more inflammatory cells infiltration into the brain, which further aggravates inflammatory brain damage [3]. However, as mentioned above, the relevant clinical trials targeting the downstream inflammatory events did not achieve significant clinical effects, which propel us to explore the upstream events that initiate the inflammatory cascade after ICH. Recently, we and others showed that microglia toll-like receptor 4 (TLR4) triggers the upstream inflammatory signal to cause secondary brain injury [5, 9, 13], which was attenuated by TLR4 antagonist TAK242 [14]. Subsequently, we found a novel TLR2/ TLR4 heterodimer triggered by Hb that initiates the excessive inflammatory responses following ICH [4], and intervening the TLR2/TLR4 heterodimer with sparstolonin B (SsnB) [15], a Chinese herb-derived compound [16], has also achieved markedly antiinflammatory effects and improved the neurologic deficit following ICH (data not published). Therefore, central excessive inflammatory responses play critical roles in the brain tissue damage after ICH, and targeting the upstream events of inflammation may provide a novel approach for the treatment of ICH.



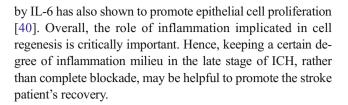
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Peripheral Inflammation Plays a Detrimental Role in the ICH-Induced Brain Injury

Sympathetic nervous system and vagus nerve link the central nervous system (CNS) to the peripheral immune system [17]. Stroke activates the sympathetic nervous system and the vagus nerve to regulate the stroke-induced immune reaction [18, 19], suggesting that in addition to indirectly activating the peripheral immune cells by the release of pro-inflammatory cytokines and DAMPs after ICH, the damage signals could directly via sympathetic nerve or vagus nerve to regulate peripheral immune cells, which through the breakdown bloodbrain barrier (BBB) and infiltrate into the brain involved in the ICH-induced inflammatory responses, and further aggravate the patient's neurologic deficit [20]. Recently, both experimental and clinical researches showed that fingolimod, a sphingosine 1-phosphate receptor (S1PR) modulator that could reduce the trafficking of lymphocyte into the CNS by inhibiting the egress from lymphoid organs and preventing their recirculation [21–24], significantly attenuated neurologic deficits and promoted recovery [25-27]. In addition, splenectomy is also beneficial in ICH-induced brain injury [28]. These results strongly indicated that the peripheral activated inflammatory responses also play an important role in the stroke-induced brain damage [29]. Although clinical research of fingolimod for the treatment of ICH did not increase infection risk [27], this approach of post-stroke immune suppression still has potential possibility to lead to increased infection rates [30]. Thus, sufficiently understanding and intervening the systematic inflammation after ICH may give a better and safe therapeutic method for the ICH patients.

Modest Inflammation is Beneficial to the Neurogenesis After ICH

As discussed above, the inflammatory cascade, undoubtedly, was one of the predominately causes for the secondary brain injury following ICH. Thus, targeting the immune responses by early intervention and treatment could be beneficial to the patients. Moreover, the late phase of recovery treatment also has a critical role for the ICH patients [31–33], and this may mainly ascribe to the neurogenesis after brain damage. Increasing evidence shows that neurogenesis is existing in the adult human brain [34, 35]. ICH induces neurogenesis in the adult human brain [35], which may be attributed to producing inflammatory cytokines, such as IL-6 to promote neuronal survival and axonal regeneration [36, 37]. Similarly, the Notch1 signaling is involved in neurogenesis after stroke [38], and neuroinflammation triggered by β-glucan/dectin-1 signaling enables CNS axon regeneration, suggesting that innate immunity has the ability to enable repair of injured CNS neurons [39]. Moreover, the gp130-Src-YAP signaling activated



Conclusions

Excessive inflammatory responses, both central and peripheral inflammation, contribute to brain injury following ICH, while modest inflammation promotes the neurogenesis. Therefore, finding out the critical targets that initiate the inflammatory cascade and giving more attention to regulating the peripheral inflammation will provide a more clear inflammatory profile to achieve better therapeutic effects for ICH. In addition, we have demonstrated that SsnB, as a Chinese herb monomer, can not only inhibit the central but also the peripheral TLRs signaling to reduce the upstream inflammatory events that caused brain injury; meanwhile, it would not change the blood immune cell quantities which avoid increasing infection risk. So, it may have a better application prospect for the ICH treatment. However, further study should perform to investigate the clinical effects of SsnB in the ICH patients, in particular, targeting the inflammatory cascade in the early stage to reduce secondary brain injury and keeping a modest inflammation milieu in the late stage to promote neurogenesis and recovery. Therefore, seeking an appropriate treatment time window for the ICH treatment may provide a better therapeutic strategy.

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Conflict of Interest The authors declare that they have no competing interest.

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