Transl. Stroke Res. (2015) 6:339–341
DOI 10.1007/s12975-015-0402-1

COMMENTARY

Rethinking the Roles of Inflammation in the Intracerebral Hemorrhage

Xiao-Yi Xiong[1] · **Qing-Wu Yang**[1]

Received: 17 April 2015 / Accepted: 21 April 2015 / Published online: 5 May 2015

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 pro-inflammatory 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), 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 pro-inflammatory cytokines such as interleukin (IL)-6, TNF-α, and IL-1β, 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 danger-associated molecular patterns (DAMPs), such as high-mobility 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 anti-inflammatory 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.

✉ Qing-Wu Yang
yangqwmlys@hotmail.com

[1] Department of Neurology, Xinqiao Hospital, the Third Military Medical University, No.183, Xinqiao Main Street, Shapingba District, Chongqing 400037, China

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 blood-brain 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 by IL-6 has also shown to promote epithelial cell proliferation [40]. Overall, the role of inflammation implicated in cell regenesis is critically important. Hence, keeping a certain degree of inflammation milieu in the late stage of ICH, rather than complete blockade, may be helpful to promote the stroke patient's recovery.

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.

Acknowledgments This work was supported by grants from the National Natural Science Foundation of China (81471191) and the National Basic Research Program of China (973 Program) (2014CB541605).

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

References

1. Wang J, Doré S. Inflammation after intracerebral hemorrhage. J Cereb Blood Flow Metab. 2007;27(5):894–908.
2. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet. 2005;365(9457):387–97.
3. Zhou Y, Wang Y, Wang J, Stetler RA, Yang QW. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. Prog Neurobiol. 2014;115:25–44.
4. Wang YC, Zhou Y, Fang H, Lin S, Wang PF, Xiong RP, et al. Toll-like receptor 2/4 heterodimer mediates inflammatory injury in intracerebral hemorrhage. Ann Neurol. 2014;75(6):876–89.

5. Fang H, Wang PF, Zhou Y, Wang YC, Yang QW. Toll-like receptor 4 signaling in intracerebral hemorrhage-induced inflammation and injury. J Neuroinflammation. 2013;10(1):27.
6. Sheth KN, Rosand J. Targeting the immune system in intracerebral hemorrhage. JAMA Neurology. 2014;71(9):1083–4.
7. Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage. Prog Neurobiol. 2010;92(4):463–77.
8. Chen S, Yang Q, Chen G, Zhang JH. An update on inflammation in the acute phase of intracerebral hemorrhage. Transl Stroke Res. 2015;6(1):4–8.
9. Lin S, Yin Q, Zhong Q, Lv FL, Zhou Y, Li JQ, et al. Heme activates TLR4-mediated inflammatory injury via MyD88/TRIF signaling pathway in intracerebral hemorrhage. J Neuroinflammation. 2012;9(1):46.
10. Xiong XY, Wang J, Qian ZM, Yang QW. Iron and intracerebral hemorrhage: from mechanism to translation. Transl Stroke Res. 2014;5(4):429–41.
11. Hatakeyama T, Okauchi M, Hua Y, Keep RF, Xi G. Deferoxamine reduces neuronal death and hematoma lysis after intracerebral hemorrhage in aged rats. Transl Stroke Res. 2013;4(5):546–53.
12. Zhou Y, Xiong KL, Lin S, Zhong Q, Lu FL, Liang H, et al. Elevation of high-mobility group protein box-1 in serum correlates with severity of acute intracerebral hemorrhage. Mediat Inflamm. 2010. doi:10.1155/2010/142458.
13. Sansing LH, Harris TH, Welsh FA, Kasner SE, Hunter CA, Kariko K. Toll-like receptor 4 contributes to poor outcome after intracerebral hemorrhage. Ann Neurol. 2011;70(4):646–56.
14. Wang YC, Wang PF, Fang H, Chen J, Xiong XY, Yang QW. Toll-like receptor 4 antagonist attenuates intracerebral hemorrhage-induced brain injury. Stroke. 2013;44(9):2545–52.
15. Xiong XY, Wang YC, Yang QW. A novel theraputic target for intracerebral hemorrhage: interfering with the TLR2/TLR4 heterodimerization. Inflamm Cell Signal. 2014;1:230–2.
16. Liang Q, Wu Q, Jiang J, Duan J, Wang C, Smith MD, et al. Characterization of sparstolonin B, a Chinese herb-derived compound, as a selective Toll-like receptor antagonist with potent anti-inflammatory properties. J Biol Chem. 2011;286(30):26470–9.
17. Trakhtenberg EF, Goldberg JL. Neuroimmune communication. Science. 2011;334(6052):47–8.
18. Wang J, Yu L, Jiang C, Fu X, Liu X, Wang M, et al. Cerebral ischemia increases bone marrow CD4+CD25+FoxP3+ regulatory T cells in mice via signals from sympathetic nervous system. Brain Behav Immun. 2015;43:172–83.
19. Rosas-Ballina M, Olofsson PS, Ochani M, Valdés-Ferrer SI, Levine YA, Reardon C, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011;334(6052):98–101.
20. Zhao X, Sun G, Zhang H, Ting SM, Song S, Gonzales N, et al. Polymorphonuclear neutrophil in brain parenchyma after experimental intracerebral hemorrhage. Transl Stroke Res. 2014;5(5):554–61.
21. Gebel JM, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, et al. Relative edema volume is a predictor of outcome in patients with hyperacute spontaneous intracerebral hemorrhage. Stroke. 2002;33(11):2636–41.
22. Massberg S, von Andrian UH. Fingolimod and sphingosine-1-phosphate—modifiers of lymphocyte migration. N Engl J Med. 2006;355(11):1088–91.
23. Schwab SR, Pereira JP, Matloubian M, Xu Y, Huang Y, Cyster JG. Lymphocyte sequestration through S1P lyase inhibition and disruption of S1P gradients. Science. 2005;309(5741):1735–9.
24. Chiba K. FTY720, a new class of immunomodulator, inhibits lymphocyte egress from secondary lymphoid tissues and thymus by agonistic activity at sphingosine 1-phosphate receptors. Pharmacol Ther. 2005;108(3):308–19.
25. Rolland WB, Lekic T, Krafft PR, Hasegawa Y, Altay O, Hartman R, et al. Fingolimod reduces cerebral lymphocyte infiltration in experimental models of rodent intracerebral hemorrhage. Exp Neurol. 2013;241:45–55.
26. Lu L, Barfejani AH, Qin T, Dong Q, Ayata C, Waeber C. Fingolimod exerts neuroprotective effects in a mouse model of intracerebral hemorrhage. Brain Res. 2014;1555:89–96.
27. Fu Y, Hao J, Zhang N, Ren L, Sun N, Li YJ, et al. Fingolimod for the treatment of intracerebral hemorrhage: a 2-arm proof-of-concept study. JAMA Neurology. 2014;71(9):1092–101.
28. Lee ST, Chu K, Jung KH, Kim SJ, Kim DH, Kang KM, et al. Anti-inflammatory mechanism of intravascular neural stem cell transplantation in haemorrhagic stroke. Brain. 2008;131(3):616–29.
29. Seifert HA, Pennypacker KR. Molecular and cellular immune responses to ischemic brain injury. Transl Stroke Res. 2014;5(5):543–53.
30. Prass K, Meisel C, Höflich C, Braun J, Halle E, Wolf T, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. J Exp Med. 2003;198(5):725–36.
31. Tamakoshi K, Ishida A, Takamatsu Y, Hamakawa M, Nakashima H, Shimada H, et al. Motor skills training promotes motor functional recovery and induces synaptogenesis in the motor cortex and striatum after intracerebral hemorrhage in rats. Behav Brain Res. 2014;260:34–43.
32. Caliaperumal J, Colbourne F. Rehabilitation improves behavioral recovery and lessens cell death without affecting iron, ferritin, transferrin, or inflammation after intracerebral hemorrhage in rats. Neurorehabil Neural Repair. 2014;28(4):395–404.
33. Chu K, Jeong SW, Jung KH, Han SY, Lee ST, Kim M, et al. Celecoxib induces functional recovery after intracerebral hemorrhage with reduction of brain edema and perihematomal cell death. J Cereb Blood Flow Metab. 2004;24(8):926–33.
34. Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, Tisdale J, et al. Neurogenesis in the striatum of the adult human brain. Cell. 2014;156(5):1072–83.
35. Shen J, Xie L, Mao X, Zhou Y, Zhan R, Greenberg DA, et al. Neurogenesis after primary intracerebral hemorrhage in adult human brain. J Cereb Blood Flow Metab. 2008;28(8):1460–8.
36. Yang P, Wen H, Ou S, Cui J, Fan D. IL-6 promotes regeneration and functional recovery after cortical spinal tract injury by reactivating intrinsic growth program of neurons and enhancing synapse formation. Exp Neurol. 2012;236(1):19–27.
37. Cafferty WB, Gardiner NJ, Das P, Qiu J, McMahon SB, Thompson SW. Conditioning injury-induced spinal axon regeneration fails in interleukin-6 knock-out mice. J Neurosci. 2004;24(18):4432–43.
38. Magnusson JP, Göritz C, Tatarishvili J, Dias DO, Smith EM, Lindvall O, et al. A latent neurogenic program in astrocytes regulated by Notch signaling in the mouse. Science. 2014;346(6206):237–41.
39. Baldwin KT, Carbajal KS, Segal BM, Giger RJ. Neuroinflammation triggered by β-glucan/dectin-1 signaling enables CNS axon regeneration. Proc Natl Acad Sci U S A. 2015;112(8):2581–6.
40. Taniguchi K, Wu LW, Grivennikov SI, de Jong PR, Lian I, Yu FX, et al. A gp130-Src-YAP module links inflammation to epithelial regeneration. Nature. 2015;519(7541):57–62.