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REVIEW ARTICLE

An Update on Inflammation in the Acute Phase of Intracerebral Hemorrhage

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Abstract Intracerebral hemorrhage (ICH) is a common and severe neurological disorder, which is associated with high rates of mortality and morbidity. Despite extensive research into the pathology of ICH, there are still no clinically approved neuroprotective treatments. Currently, increasing evidence has shown that inflammatory responses participate in the pathophysiological processes of brain injury following ICH. In this editorial, we summarized some promising advances in the field of inflammation and ICH, which contained animal and human investigations; discussed the role of neuroinflammation, systemic inflammatory responses, and some potential targets; and focused on the challenges of translation between pre-clinical and clinical studies and potential anti-inflammatory therapeutic approaches after ICH.

Keywords Intracerebral hemorrhage · Inflammation · Brain injury

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Intracerebral hemorrhage (ICH) refers to the condition in which weakened blood vessels in the brain suddenly rupture and blood flows into the surrounding brain parenchyma [1, 2]. ICH accounts for 10–15 % of all strokes in the USA, Europe, and Australia, with high morbidity and mortality [3]. Clinical management of ICH lacks a consensus-based standard strategy and varies significantly along the spectrum of this illness throughout the world.

Brain injury after ICH is broadly divided into primary brain injury and secondary brain injury. After sudden rupture of the cerebral blood vessels, hematoma rapidly forms in the brain tissues and compresses surrounding brain tissues, leading to a sharp increase in intracranial pressure, which causes primary brain injury [4]. Acute resuscitation for ICH patients aimed at removing mass effect, preventing hematoma growth (blood pressure control and reversal of coagulopathy) and optimizing brain perfusion (including control of high intracranial pressure). At present, surgical removal of the hematoma treatment targeting primary brain injury after ICH has shown only minimal effects in neurological recovery. The Surgical Trial in Intracerebral Haemorrhage (STICH) was unable to show an overall benefit from "early surgery" compared with a policy of "initial conservative treatment" [5]. Furthermore, the Surgical Trial in Intracerebral Hemorrhage (STICH II) results confirmed that there was no significant difference in mortality and prognosis between early surgery group and conservative treatment group [6]. So far, some multicenter, randomized, controlled trials targeting on the primary brain injury are still ongoing, such as ICH ADAPT (*NCT00963976*), MISTIE III (*NCT01827046*), and SWITCH (*NCT02258919*). Secondary brain injury following ICH is mediated by primary injury (e.g., mass effect, high intracranial pressure, and mechanical stress), as well as physiological response to the hematoma and the products of hematoma degradation, such as inflammation. Most of the past experimental studies focused on the prevention and treatment of secondary brain injury after ICH.

Neuroinflammation contributes to the pathophysiology of diverse diseases, such as stroke, traumatic brain injury, Alzheimer's disease, and Parkinson's disease [7, 8]. The evidences from randomized controlled trials supported a beneficial effect of inflammation inhibition in several central nervous system diseases, including multiple sclerosis and traumatic brain injury [9, 10]. In ICH, inflammation begins immediately after the formation of hematoma and increasing evidence has shown that inflammation is one of the crucial contributors of ICH-induced secondary brain injury. The mechanisms of ICH-induced brain injury mediated by inflammation are complex and involved multiple signaling pathways. Since the inflammatory response is an important factor causing brain injury after ICH, resulting in loss of neurological function, anti-inflammation might be a potential treatment for the patients with ICH. Pre-clinical experiments have confirmed that inhibition of the inflammatory responses was an effective approach to treat ICH. However, clinical trials of those drugs are rarely successful, especially in prospective randomized, controlled, double-blinded studies.

Early inflammatory reactions after ICH include accumulation of the inflammatory substance released by inflammatory cells. Under normal conditions, microglia exert a neuroprotective role in the brain. After ICH, microglia was rapidly activated within minutes of the onset of bleeding. Microglia represented the primary phagocytic system that promoted the cleanup of hematoma with the assistance of Nrf2 or peroxisome proliferator-activated receptor (PPARg) pathways and prevented other brain cells from ICH-induced damage [11, 12]. However, excessive microglia were activated by the products of hematoma degradation, which initiated the cascade of inflammatory signaling pathways and played a key role in releasing cytokines, chemokines, free radicals, and other toxic chemicals, eventually aggravated ICH-induced brain injury. The inflammatory cytokines mainly include interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α). The activation of nuclear factor-κB was enhanced, and the production of IL-1β, IL-6, and metalloproteinase-9 were increased at 1 and 3 days after ICH in rat's brain [13, 14]. The anti-inflammatory agent prevented blood–brain barrier disruption and perihematomal edema development via decreasing cytokines after ICH [15]. For the upstream of those inflammatory molecules, inflammasomes are intracellular protein complexes that play an important role in regulating inflammation [16]. NLRP3 inflammasomes promote the maturation and secretion of pro-inflammatory cytokines after ICH, such as IL-1β and IL-18 [17]. Hence, inhibiting inflammasome might be a promising therapeutic strategy for treating ICH. In addition, the chemokines and their receptors were associated with the pathophysiology of ICH. The analysis of brain tissue has indicated that chemokine receptors and their downstream effector molecules were activated after ICH [18]. In a collagenase injection ICH model, prominent upregulation of mRNAs for CXCL1, CXCL2, and CCL3 was observed [19]. In 85 patients with ICH, higher CCL2 levels at 24 h were independently associated with poor functional outcome at day 7 [20]. Similarly, after ICH, blood-derived CCR2+Ly6C (hi) inflammatory monocytes trafficked into the brain in larger quantity than other leukocytes in mice, and increased TNF expression [20]. Ccr2 (−/−) mice exhibited better motor function than wild-type mice after ICH. In a swine model of ICH, CD47 expression was upregulated in the perihematomal white and gray matter at 4 h to 14 days after ICH, which was decreased by deferoxamine [21]. Hence, better understanding of neuroinflammation could shed light on the development of effective treatments for ICH.

Recruitment and infiltration of inflammatory cells, such as monocytes, macrophages, neutrophils, and lymphocytes, into brain parenchyma is the key step of inflammation initiation and progression [22, 8]. After the lesion vessels rupture, red blood cells, white blood cells (WBC), plasma proteins such as thrombin, and other substances permeated into the surrounding brain parenchyma and activated inflammatory cells, such as resident microglia [23–25]. Recently, two retrospective clinical studies have shown that WBC count in the peripheral blood independently reflected long-term functional outcome of the patients with ICH, suggesting that activation of the peripheral immune system aggravated brain damage after ICH. Within 72 h after ictus of ICH, if WBC count in the peripheral blood was more than 10,000/mL^3, there was a relatively high possibility of early neurological deterioration. WBC counts increase was correlated with the midline shift [26, 27]. A multicenter prospective study demonstrated that the levels of IL-6, TNF-α, matrix metalloproteinase-9, and cellular fibronectin in the serum of patients with ICH were significantly higher than in controls and were highly associated with hematoma volume [28]. α4 integrin, as an important cell adhesion molecule, was elevated on all leukocyte populations in a blood injection mouse model of ICH, which suggested α4 integrin was involved in inflammation. Blocking α4 decreased leukocyte transmigration and lessened neurobehavioral disability after ICH [29]. More recently, T cell immunoglobulin and mucin domain-3 (Tim-3) increased in the early phage in mouse perihematomal brain tissue with a peak at day 1, which was positively correlated with the concentrations of TNF-α, IL-1β, and brain water content [30]. Fingolimod, a sphingosine 1-phosphate receptor analog, ameliorated cerebral inflammation, reduced perihematomal edema, and improved neurological outcome, by preventing brain infiltration of T lymphocytes in experimental and clinical ICH [31, 23]. In another retrospective study, the relatively higher level of mononuclear cells in the peripheral blood of ICH patients was closely associated with mortality within 3 months [32]. In an experimental study, removal of the spleen was beneficial in hemorrhagic stroke-induced brain injury by targeting the peripheral inflammatory cells [33], but additional

studies are needed to translate these exciting findings into clinical setting.

The components of hematomas, including red blood cells, the products of their degradation (hemoglobin, heme, and iron ions), and thrombin all promote inflammation [4]. Toll-like receptors (TLRs) not only recognize the molecular signals of different pathogens, but also receive death signals and activate the immune responses, leading to tissue damage [34]. After ICH, TLRs were activated by the components of hematomas, which played a key role in innate immunity and inflammatory responses after ICH. TLR2 and TLR4 are expressed on several cells in the central nervous system, including microglia, astrocytes, neurons, and endothelial cells. TLR2 and TLR4 signaling pathways were crucial to ICH-mediated inflammation, and TLR antagonists were used to attenuate brain injury via inhibiting inflammatory response after ICH [35, 36]. TLR4 mRNA and protein expression levels started to increase in the first few hours after ICH and reached a peak level within 3 days. Heme from blood activated TLR4 for activation of microglia, which aggravated inflammatory injury. TLR4 inhibition promoted hematoma absorption via increasing CD36 expression in microglia and significantly improved neurologic deficits following ICH [37]. A recent clinical trial showed overexpression of TLR2 and TLR4 on the peripheral mononuclear cell membranes of patients with ICH at admission to be closely associated with their prognosis [38]. TLR4 antagonists include TAK-242, curcumin, zingiberene phenol, and isoliquiritigenin [35]. However, the clinical beneficial effects of those drugs need to be further investigated [39]. Taken together, the above evidence suggested inhibition of TLR would be a potential therapeutic intervention. In addition, after ICH, some intracellular molecules directly stimulated the inflammatory reaction. For instance, high-mobility group protein box-1 (HMGB1) is a pro-inflammatory molecule released from necrotic cells. A case–control study demonstrated that HMGB1 expression in the serum of acute phase ICH patients was significantly upregulated, which were closely associated with inflammatory brain injury after ICH and the severity of the patients [40]. To reduce the toxicity of these products, preclinical studies have used PPARg agonists to promote hematoma degradation, and haptoglobin and deferoxamine were also used to combat the toxicity of hemoglobin/heme and iron originated from extravascular hemolysis and heme oxygenase-mediated catabolism [41, 12]. Currently, a prospective, randomized, placebo-controlled, dose-dependent clinical trial, called Safety of Pioglitazone for Hematoma Resolution in Intracerebral Hemorrhage (SHRINC, *NCT00827892*), is under way. Its purpose is to assess the effectiveness and safety of PPARg agonist rosiglitazone in clinical practice [42]. Another method for reducing the severity of inflammatory brain injury after ICH is to chelate iron [43–45]. Phase I clinical trials have confirmed that desferrioxamine as a treatment of ICH was feasible and safe. However, intravenous injection of deferoxamine mesylate at 62 mg/kg for Hi-DEF has been suspended due to increased incidence of acute respiratory distress syndrome. Thus, Intracerebral Hemorrhage Deferoxamine Trial—iDEF Trial (*NCT02175225*), which aim to determine whether deferoxamine mesylate treatment is sufficient to improve outcome before pursuing a larger clinical trial to examine its effectiveness as a treatment for ICH, is ongoing.

It is noteworthy that although anti-inflammatory may ameliorate the acute brain injury after ICH, one side effect with this approach is the potentiation of the immune suppression, which results in higher infection rates [33]. Besides, inflammation and immune cells are crucial to the repair and regeneration of brain tissue during the late stage [46–48]. Long-term suppression of inflammation may affect brain tissue repair in the late stage of ICH, and this is worrisome. Unfortunately, until now, there are no experiments investigating the long-term effects of anti-inflammatory drugs during convalescence [4]. It may be predicted that, based on careful selection of patients for enrollment in ongoing trials, combination therapies including early administration of anti-inflammation agents and surgical evacuation could also be pursued.

In summary, these timely studies revealed a critical role of inflammation in the mechanism of ICH-induced brain injury. Anti-inflammatory may be a potential strategy for drug design and development for the patients with ICH. Therefore, further investigation of inflammation after ICH is highly warranted.

Compliance with Ethics Requirements The study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. This article does not contain any studies with human or animal subjects.

Conflict of Interest Sheng Chen declares that he has no conflict of interest. Qingwu Yang declares that he has no conflict of interest. Gang Chen declares that he has no conflict of interest. John H. Zhang declares that he has no conflict of interest.

References

1. Pandey AS, Xi G. Intracerebral hemorrhage: a multimodality approach to improving outcome. Transl Stroke Res. 2014;5(3):313–5. doi:10.1007/s12975-014-0344-z.
2. Chen Q, Zhang J, Guo J, Tang J, Tao Y, Li L, et al. Chronic hydrocephalus and perihematomal tissue injury developed in a rat model of intracerebral hemorrhage with ventricular extension. Transl Stroke Res. 2014. doi:10.1007/s12975-014-0367-5.
3. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. Lancet Neurol. 2012;11(8):720–31. doi:10.1016/S1474-4422(12)70104-7.
4. Zhou Y, Wang Y, Wang J, Anne Stetler R, Yang QW. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. Prog Neurobiol. 2014;115:25–44. doi:10.1016/j.pneurobio.2013.11.003.
5. 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. doi:10.1016/S0140-6736(05)17826-X.

6. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet. 2013;382(9890):397–408. doi:10.1016/S0140-6736(13)60986-1.
7. Wu L, Walas S, Leung W, Sykes DB, Wu J, Lo EH, et al. Neuregulin1-beta decreases IL-1beta-induced neutrophil adhesion to human brain microvascular endothelial cells. Transl Stroke Res. 2014. doi:10.1007/s12975-014-0347-9.
8. An C, Shi Y, Li P, Hu X, Gan Y, Stetler RA, et al. Molecular dialogs between the ischemic brain and the peripheral immune system: dualistic roles in injury and repair. Prog Neurobiol. 2014;115:6–24. doi:10.1016/j.pneurobio.2013.12.002.
9. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Khodadadi B, Jazayeri S, et al. Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. Nutr Neurosci. 2014. doi:10.1179/1476830513Y.0000000106.
10. Theadom A, Mahon S, Barker-Collo S, McPherson K, Rush E, Vandal AC, et al. Enzogenol for cognitive functioning in traumatic brain injury: a pilot placebo-controlled RCT. Eur J Neurol Off J Eur Fed Neurol Soc. 2013;20(8):1135–44. doi:10.1111/ene.12099.
11. Zhao X, Sun G, Ting SM, Song S, Zhang J, Edwards NJ, et al. Cleaning up after ICH: the role of Nrf2 in modulating microglia function and hematoma clearance. J Neurochem. 2014. doi:10.1111/jnc.12974.
12. Zhao X, Sun G, Zhang J, Strong R, Song W, Gonzales N, et al. Hematoma resolution as a target for intracerebral hemorrhage treatment: role for peroxisome proliferator-activated receptor gamma in microglia/macrophages. Ann Neurol. 2007;61(4):352–62. doi:10.1002/ana.21097.
13. Zhou QB, Jin YL, Jia Q, Zhang Y, Li LY, Liu P, et al. Baicalin attenuates brain edema in a rat model of intracerebral hemorrhage. Inflammation. 2014;37(1):107–15. doi:10.1007/s10753-013-9717-9.
14. Sun H, Tang Y, Guan X, Li L, Wang D. Effects of selective hypothermia on blood–brain barrier integrity and tight junction protein expression levels after intracerebral hemorrhage in rats. Biol Chem. 2013;394(10):1317–24. doi:10.1515/hsz-2013-0142.
15. Yang Z, Zhao T, Zou Y, Zhang JH, Feng H. Curcumin inhibits microglia inflammation and confers neuroprotection in intracerebral hemorrhage. Immunol Lett. 2014;160(1):89–95. doi:10.1016/j.imlet.2014.03.005.
16. Baroja-Mazo A, Martin-Sanchez F, Gomez AI, Martinez CM, Amores-Iniesta J, Compan V, et al. The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. Nat Immunol. 2014;15(8):738–48. doi:10.1038/ni.2919.
17. Ma Q, Chen S, Hu Q, Feng H, Zhang JH, Tang J. NLRP3 inflammasome contributes to inflammation after intracerebral hemorrhage. Ann Neurol. 2014;75(2):209–19. doi:10.1002/ana.24070.
18. Yao Y, Tsirka SE. Chemokines and their receptors in intracerebral hemorrhage. Transl Stroke Res. 2012;3 Suppl 1:70–9. doi:10.1007/s12975-012-0155-z.
19. Matsushita H, Hijioka M, Ishibashi H, Anan J, Kurauchi Y, Hisatsune A, et al. Suppression of CXCL2 upregulation underlies the therapeutic effect of the retinoid Am80 on intracerebral hemorrhage in mice. J Neurosci Res. 2014;92(8):1024–34. doi:10.1002/jnr.23379.
20. Hammond MD, Taylor RA, Mullen MT, Ai Y, Aguila HL, Mack M, et al. CCR2+ Ly6C(hi) inflammatory monocyte recruitment exacerbates acute disability following intracerebral hemorrhage. J Neurosci Off J Soc Neurosci. 2014;34(11):3901–9. doi:10.1523/JNEUROSCI.4070-13.2014.
21. Zhou X, Xie Q, Xi G, Keep RF, Hua Y. Brain CD47 expression in a swine model of intracerebral hemorrhage. Brain Res. 2014;1574:70–6. doi:10.1016/j.brainres.2014.06.003.
22. Hosaka K, Hoh BL. Inflammation and cerebral aneurysms. Transl Stroke Res. 2014;5(2):190–8. doi:10.1007/s12975-013-0313-y.
23. 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. doi:10.1016/j.expneurol.2012.12.009.
24. 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. doi:10.1007/s12975-014-0341-2.
25. Wu LJ. Microglial voltage-gated proton channel Hv1 in ischemic stroke. Transl Stroke Res. 2014;5(1):99–108. doi:10.1007/s12975-013-0289-7.
26. Agnihotri S, Czap A, Staff I, Fortunato G, McCullough LD. Peripheral leukocyte counts and outcomes after intracerebral hemorrhage. J Neuroinflammation. 2011;8:160. doi:10.1186/1742-2094-8-160.
27. Sun W, Peacock A, Becker J, Phillips-Bute B, Laskowitz DT, James ML. Correlation of leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage. J Clin Neurosci Off J Neurosurg Soc Australas. 2012;19(8):1096–100. doi:10.1016/j.jocn.2011.11.020.
28. Silva Y, Leira R, Tejada J, Lainez JM, Castillo J, Davalos A. Molecular signatures of vascular injury are associated with early growth of intracerebral hemorrhage. Stroke J Cereb Circ. 2005;36(1):86–91. doi:10.1161/01.STR.0000149615.51204.0b.
29. Hammond MD, Ambler WG, Ai Y, Sansing LH. alpha4 integrin is a regulator of leukocyte recruitment after experimental intracerebral hemorrhage. Stroke J Cereb Circ. 2014;45(8):2485–7. doi:10.1161/STROKEAHA.114.005551.
30. Xu C, Wang T, Cheng S, Liu Y. Increased expression of T cell immunoglobulin and mucin domain 3 aggravates brain inflammation via regulation of the function of microglia/macrophages after intracerebral hemorrhage in mice. J Neuroinflammation. 2013;10:141. doi:10.1186/1742-2094-10-141.
31. 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 Neurol. 2014;71(9):1092–101. doi:10.1001/jamaneurol.2014.1065.
32. Adeoye O, Walsh K, Woo JG, Haverbusch M, Moomaw CJ, Broderick JP, et al. Peripheral monocyte count is associated with case fatality after intracerebral hemorrhage. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2014;23(2):e107–11. doi:10.1016/j.jstrokecerebrovasdis.2013.09.006.
33. Pennypacker KR. Targeting the peripheral inflammatory response to stroke: role of the spleen. Transl Stroke Res. 2014;5(6):635–7. doi:10.1007/s12975-014-0372-8.
34. Heiman A, Pallottie A, Heary RF, Elkabes S. Toll-like receptors in central nervous system injury and disease: a focus on the spinal cord. Brain Behav Immun. 2014. doi:10.1016/j.bbi.2014.06.203.
35. Wang YC, Wang PF, Fang H, Chen J, Xiong XY, Yang QW. Toll-like receptor 4 antagonist attenuates intracerebral hemorrhage-induced brain injury. Stroke J Cereb Circ. 2013;44(9):2545–52. doi:10.1161/STROKEAHA.113.001038.
36. 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. doi:10.1002/ana.24159.
37. Fang H, Chen J, Lin S, Wang P, Wang Y, Xiong X, et al. CD36-mediated hematoma absorption following intracerebral hemorrhage: negative regulation by TLR4 signaling. J Immunol. 2014;192(12):5984–92. doi:10.4049/jimmunol.1400054.

38. Rodriguez-Yanez M, Brea D, Arias S, Blanco M, Pumar JM, Castillo J, et al. Increased expression of Toll-like receptors 2 and 4 is associated with poor outcome in intracerebral hemorrhage. J Neuroimmunol. 2012;247(1–2):75–80. doi:10.1016/j.jneuroim.2012.03.019.
39. Shin HJ, Youn HS. TBK1-targeted suppression of TRIF-dependent signaling pathway of Toll-like receptors by helenalin. Life Sci. 2013;93(22):847–54. doi:10.1016/j.lfs.2013.09.004.
40. 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.
41. Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. Stroke J Cereb Circ. 2011;42(6):1781–6. doi:10.1161/STROKEAHA.110.596718.
42. Gonzales NR, Shah J, Sangha N, Sosa L, Martinez R, Shen L, et al. Design of a prospective, dose-escalation study evaluating the Safety of Pioglitazone for Hematoma Resolution in Intracerebral Hemorrhage (SHRINC). Int J Stroke Off J Int Stroke Soc. 2013;8(5):388–96. doi:10.1111/j.1747-4949.2011.00761.x.
43. Cheng Y, Xi G, Jin H, Keep RF, Feng J, Hua Y. Thrombin-induced cerebral hemorrhage: role of protease-activated receptor-1. Transl Stroke Res. 2014;5(4):472–5. doi:10.1007/s12975-013-0288-8.
44. Xiong XY, Wang J, Qian ZM, Yang QW. Iron and intracerebral hemorrhage: from mechanism to translation. Transl Stroke Res. 2014;5(4):429–41. doi:10.1007/s12975-013-0317-7.
45. Zhao J, Chen Z, Xi G, Keep RF, Hua Y. Deferoxamine attenuates acute hydrocephalus after traumatic brain injury in rats. Transl Stroke Res. 2014;5(5):586–94. doi:10.1007/s12975-014-0353-y.
46. Shichita T, Ito M, Yoshimura A. Post-ischemic inflammation regulates neural damage and protection. Front Cell Neurosci. 2014;8:319. doi:10.3389/fncel.2014.00319.
47. Hu X, Leak RK, Shi Y, Suenaga J, Gao Y, Zheng P, et al. Microglial and macrophage polarization-new prospects for brain repair. Nat Rev Neurol. 2014. doi:10.1038/nrneurol.2014.207.
48. Hu X, Liou AK, Leak RK, Xu M, An C, Suenaga J, et al. Neurobiology of microglial action in CNS injuries: receptor-mediated signaling mechanisms and functional roles. Prog Neurobiol. 2014;119–120:60–84. doi:10.1016/j.pneurobio.2014.06.002.