Strategies to Promote Neural Regeneration after Intracerebral Hemorrhage

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The restorative capability of the central nervous system (CNS) after ICH has received little attention, even though it is clear that the brain has capacity for repair after injury. The dynamic changes of myelin (de- and remyelination) can be found in brains of patients with multiple sclerosis and Alzheimer's disease; a novel transgenic reporter mouse line shows proof of myelin renewal in normal homeostasis. Enhanced neural regenerative processes including neurogenesis, angiogenesis, oligodendrogenesis, and axonal regeneration have been observed in divergent CNS pathologies.

intracerebral hemorrhage | tissue regeneration | neurogenesis | remyelination | angiogenesis | neuroinflammation | stem cells | rehabilitation

1. Introduction

Intracerebral hemorrhage (ICH) accounts for 12–20% of all types of stroke with over 2 million individuals worldwide being afflicted annually [1]. ICH has catastrophic outcomes with up to 50% mortality and 70% disability among the survivors a year after onset [2]. A study of global disease burden shows that ICH cases have increased by 47% over the past 20 years, occurring mostly in low-income and middle-income countries [3]. This life-threatening stroke subtype can be induced by a variety of causes, including hypertension, cerebral amyloid angiopathy, trauma, vascular malformations, tumors, premature birth, and with certain drugs [4]. Even though the development of minimally invasive surgery targeting the primary injury has alleviated neurological deficits or reduced mortality [5][6][7], the prognosis of ICH remains unsatisfactory. Accordingly, scholars have turned their focus on mitigating ICH-induced inflammation and consequent secondary brain injury with significant promise preclinically and some results being clinically translated [8].

The restorative capability of the central nervous system (CNS) after ICH has received little attention, even though it is clear that the brain has capacity for repair after injury [9][10][11]. The dynamic changes of myelin (de- and remyelination) can be found in brains of patients with multiple sclerosis and Alzheimer's disease [12][13]; a novel transgenic reporter mouse line shows proof of myelin renewal in normal homeostasis [14]. Enhanced neural regenerative processes including neurogenesis, angiogenesis, oligodendrogenesis, and axonal regeneration have been observed in divergent CNS pathologies [15][16][17]. Moreover, it is commonly observed that patients with ICH gradually recover some neurofunctional deficits several months after the stroke [18]. Such a phenomenon suggests that reorganization or regeneration of neural elements occurs after ICH, giving optimism that tissue recovery in ICH

may be promoted to improve its prognosis. To achieve this goal, the regenerative events in ICH at the cellular and molecular level, and the mechanisms thereof, must be better understood.

2. Medications

Statins have been widely used to prevent ischemic stroke [19][20], but concerns about increasing the risk of ICH remain [21][22]. However, growing evidence suggests that statin use in primary or secondary prevention of ischemic stroke does not elevate the risk of acquiring ICH [23][24][25]. The ongoing SATURN trial may resolve the safety of statins in ICH patients. Interestingly, a pilot study reported lower mortality of ICH patients in the rosuvastatin treatment group [26]. Additional data from a cohort study lasting 10 years in Denmark report that stroke-free statin users had a 22–35% lower risk for ICH compared to reference subjects [25]. In preclinical ICH, the results of statin treatment are usually beneficial. In an autologous blood induced model, simvastatin or atorvastatin given to rats daily for 1 week post-injury augments the number of DCX^+ neural precursor cells and $BrdU^+$ proliferating cells along with better neurological functions compared to controls at 28 days; ameliorated tissue loss at this time point is observed by both MRI and histology [27]. In the same model, enhanced neurogenesis and synaptogenesis is reported by an earlier study that shows increased DCX, synaptophysin and TUJ 1 positive cells with treatment of statin [28]. Statin is also documented to stimulate the generation of VEGF, BDNF, and NGF, which may facilitate repair after ICH through neurotrophic ways [29]. Angiogenesis and revascularization can be promoted by statin in rat model, observed in both histology and MRI [30]. In another study, statin was found to stimulate “M2”-like polarization of microglia with enhanced phagocytosis function, which promotes hematoma and iron clearance, leading to better tissue and functional recovery [31]. Moreover, statin may act as a immunomodulator to inhibit excessive inflammatory response in the early phase after experimental ICH to limit secondary brain injury [8].

Minocycline is often tested as a microglia inhibitor to control injurious neuroinflammation soon after experimental ICH where it displays various therapeutic effects [32][33][34]. The inhibition of proinflammatory microglia phenotype seemingly does not interfere with the regulatory properties of microglia [35]. In autologous blood induced ICH rats, administration of minocycline facilitates an “M2”-like polarization and increases microglia-derived BDNF; enhanced neurogenesis is observed with more DCX and Tuj-1 positive neuron-like cells than in a control group at 24 h after ICH onset [36]. Another study reported NGF elevation by minocycline after collagenase ICH [37]. However, minocycline injection is documented to inhibit angiogenesis by downregulating the level of VEGF and its receptors after experimental ICH, which may hinder tissue regeneration in the late phase [38]. For now, all completed clinical trials demonstrate safety but not efficacy of minocycline treatment for cerebral hemorrhage [39][40], although the studies are not powered for efficacy. The roles and usage of minocycline in ICH still need more investigation from both clinical and preclinical work.

Four of five sphingosine-1-phosphate receptors (S1PR1, S1PR2, S1PR3, and S1PR5) are found expressed at different levels in divergent neural cells of the CNS. S1PR1 activation is reported to be linked to neuronal growth, reduced proinflammatory microglial activity, and myelin formation, while S1PR5 signaling assists mature oligodendrocyte survival [41]. A multiple S1PRs modulator, fingolimod, is shown to elevate neurotrophic factors including BDNF and GDNF in cultured microglia, and to promote regulatory polarization while inhibiting the

proinflammatory property of microglia in an ischemic model [42][43]. In mice with collagenase induced ICH, 4 weeks of fingolimod treatment post-injury significantly improves white matter integrity, neuronal survival, and functional performance at 28 days without altering lesion volume at 5 days [44], which implies that fingolimod facilitates tissue repair in the later phase. It would be reasonable to hypothesize that S1PRs modulators may contribute to regenerative processes including neurogenesis and remyelination after ICH, but direct evidence is lacking. Although many data show that S1PR modulators improve functional recovery in different ICH models, the studies have focused on inhibition of harmful neuroinflammation [45][46][47][48] that can lead to secondary improvement. A proof-of-concept clinical study documented reduced perihematomal edema and better functional recovery after oral administration of fingolimod for three days post-onset comparing to patients with standard care [49].

Siponimod is a selective S1PR modulator predominantly binding to S1PR1 and S1PR5 [41], which may generate more protective effects and a less adverse reaction in ICH. The therapeutic effects of siponimod have been demonstrated in both collagenase and autologous blood models of ICH, but these studies did not address tissue repair [36][50][51]. A phase II randomized, placebo-controlled, double-blind clinical trial of siponimod in ICH patients is ongoing but temporarily suspended due to COVID-19.

Lithium, a mood stabilizer for bipolar disorders [52], was recently shown to be beneficial in preclinical ICH. Intraperitoneal administration of lithium chloride immediately after ICH induction promotes the “M2”-like polarization of microglia with enhanced phagocytosis and hematoma resolution within first 7 days post-injury; elevated levels of VEGF and BDNF that may contribute to angiogenesis and neurogenesis are documented in the subsequent 7 days [53]. Lithium has also been found to alleviate white matter injury including demyelination, axonal degeneration, and death of oligodendrocytes in the autologous blood ICH model, correspondent with upregulated BDNF level [54]; it is uncertain whether lithium chloride promotes white matter repair or protects from injury.

CD47, an integrin-associated protein expressed on erythrocytes, has been demonstrated to regulate hematoma clearance in the ICH model [55]. A blocking antibody to CD47 improves behavioral performance while reducing lesion volume by boosting M/M-induced erythrophagocytosis after experimental ICH [56][57].

Neurotrophins are essential and beneficial for tissue repair after brain injury, but exogenous neurotrophic factors are hard to sustain at a therapeutic concentration in the lesion area; chemical modifications may resolve this problem. Brain-derived neurotrophic factor (BDNF) fused to a collagen-binding domain could stimulate neurogenesis and angiogenesis better than natural BDNF and it maintains the growth factor at a higher level in the injured hemisphere after injection into the lateral ventricle of rats with ICH [58]. Exogenous fibrin-binding domain fused BDNF is observed to concentrate in the perihematomal area and to promote neural regeneration with ameliorated neurological deficits [59]. Moreover, there is a proof-of-concept study that administration of mouse nerve growth factor improves 3 month functional recovery compared to citicoline controls in patients with spontaneous ICH [60].

3. Stem Cell Therapy

As a promising strategy to improve the dismal prognosis, stem cells and related therapies remain popular in the realm of ICH research, and they have safety and improved functional outcomes in several clinical trials [61][62][63][64]. The therapeutic effects of stem cells could mainly be attributed to cell replacement proliferation and differentiation to neurons or glial cells, and/or the paracrine secretion of multiple neurotrophins and regulatory molecules [65][66][67] to assist immunoregulation, neural cell survival, and tissue repair, after CNS injury [68][69][70][71]. In preclinical studies, the administration of different types of stem cells or their products is observed to promote neural regeneration and recovery.

Mesenchymal stem cells (MSCs) are the most widely used cell type in research of ICH treatment [72]; they reduce lesion volume and inflammation while increasing angiogenesis, tissue repair, and functional recovery in different animal models of ICH [73]. Bone-marrow-derived mesenchymal stem cell (BMSC) transplants proliferate and differentiate into neural cells and increases the level of BDNF after collagenase induced ICH [74]. Axonal sprouting and regeneration, and improved functional recovery, are enhanced by transplantation in the same model [75]. In the hemoglobin-induced ICH model, BMSC grafts increase $NeuN^+$ (marker of mature neuron) cells and upregulate ZO-1 (a part of tight junction) expression as well as decreasing inflammatory response [76]. BM-MSCs are also observed to promote axonal regeneration in the autologous blood ICH model, which might be mediated by activating ERK1/2 and PI3K/Akt signaling pathways [77].

Some researchers have tried to facilitate the therapeutic effects of stem cells by genetic manipulation. Glial cell line-derived neurotrophic factor (GDNF) plays a crucial role in differentiation, survival, and repair in CNS [78][79][80]. GDNF transfected MSCs express neural cell-specific biomarkers including NSE, MAP2, and GFAP after implantation into ICH rats which leads to better behavioral performance than parental MSCs [81]. Moreover, overexpression of microRNA-126a-3p in BM-MSCs appears to repair the blood–brain barrier by differentiating to $CD31^+$ endothelial cells and upregulating ZO-1 and claudin-5 (both tight junction proteins) after ICH in rats [82].

Multi-lineage differentiating stress enduring (Muse) cell, a novel type of non-tumorigenic pluripotent stem cell, shows high potential for tissue regeneration and lesional navigation, and can be collected from cultured mesenchymal stem cells by stage-specific embryonic antigen 3 and CD105 double-positive sorting [83][84][85]. In the autologous blood-induced ICH model of mice, human Muse cells administrated into the hematoma cavity 5 days after injury survived well and led to better functional recovery than MSC controls at day 69, associated with significantly higher ratio of NeuN (57%) and MAP2 (41.6%) [86].

Adipose-derived stem cell (ADSC) is also a member of mesenchymal stem cells. Intravenous injection of human ADSCs in the acute phase after experimental ICH results in alleviated neurological deficits during the subacute phase [87]. Cerebral ventricle administrated ADSCs are observed to differentiate into neuron-like and astrocyte-like cells and upregulate VEGF level as well as promoting neurological functions [88]. Brain edema and tissue damage are reduced by ADSCs implantation in another ICH model [89]. CX3CR1 is a receptor of the chemokine fractalkine [90][91][92]. Overexpression of CX3CR1 of ADSCs facilitates the migration ability of engrafted cells to the perihematomal region of ICH mice and improves scores in behavioral tests compared to naïve stem cells [93]. Umbilical tissue can be another resource for mesenchymal stem cells. Intravenous administration of umbilical cord-

derived stem cells (UCSC) improves neurogenesis (marked by BrdU, TUJ1, DCX, NeuN and synaptophysin) and angiogenesis (marked by vWF) as well as motor functions after autologous blood injection into rat striatum [94]. In addition, intraventricular engraftment of hepatocyte growth factor transfected UCSCs 1 week after collagenase-ICH promotes tissue repair and neurological recovery by remyelination and axonal regeneration [95].

Neural stem cells (NSCs) and induced pluripotent stem cells (iPSCs) were commonly studied in ICH treatment about 10–20 years ago [72]. A result published in 2003 showed that intravenous administration of human NSCs one day after collagenase-induced ICH in rodents exhibited better functional performance with injected cells migrating to the injury region where 10% differentiated to neuron-like cells, whereas 75% became glia [96]. Applying immortalized human NSCs and intracerebral delivery seems to increase neural-like differentiation (30–40%) of engrafted cells [97]. Moreover, intracerebral transplantation of fetal neural stem cells or cell-conditioned medium both improve neurological function [98]. Intracerebral implantation of iPSCs promotes functional recovery and reduces neuronal death after experimental ICH, but engrafted cells predominantly differentiate to GFAP positive astrocytes [99]; conversely, human iPSCs derived neuroepithelial-like stem cells mature and transform into neurons in the post-ICH microenvironment [100].

Disadvantages of iPSCs include high tumorigenic risks [101], and NSCs may be harder to prepare and proliferate than other stem cell populations, which could be the reason why they are not that popular in ICH research today. Recently, stem cell-derived exosomes, the main component of therapeutic paracrine mechanisms, which contain proteins, RNAs, and lipids that might mediate tissue repair and immunomodulation after CNS injury, are attracting more interest [102][103]. In preclinical studies of ICH, intravenous administration of MSC-derived exosomes dramatically promotes white matter repair, axonal sprouting, and functional restoration [104]. Another study reports that injection of proteins from MSC-derived exosomes increased myelin coverage and endothelial cells in the perihematomal area as well as neuroblasts and mature neurons in the subventricular zone after blood injection induced ICH; both cognitive and sensorimotor function are restored by the treatment [105]. Furthermore, exosomes derived from genetic modified MSCs also promote functional recovery and neural survival [106][107].

Exosomes are easier to prepare and store in large amounts and have a lower potential for tumorgenicity, immunogenicity, and thrombosis than stem cells, making them more feasible in clinical application. However, their therapeutic effects might be restricted because exosomes cannot play a part in direct tissue replacement that may be crucial in regeneration after ICH. In general, stem cells and their products are highly promising for translation and improve the dismal prognosis of ICH, but challenges include safety, type, timepoint, dosage, and mode of delivery.

4. Biomaterials and Nanoparticles

The interdisciplinary cooperation between material science and medicine has become common, including for ICH. Hydrogel is considered a biocompatible material that can be injected during minimally invasive surgery and form a matrix for cell infiltration and adhesion to facilitate tissue repair after stroke [108][109]. Gelatin hydrogel injection into the lesion three days post collagenase-induced ICH is reported to alleviate neurological deficits of mice due to

conversion of M/M from pro-inflammatory to regulatory [110]. Moreover, hydrogels may carry medications, neurotrophic factors, and stem cells as well as receive chemical modifications to enhance therapeutic effects [109][111]. Hydrogel containing epidermal growth factor (EGF) significantly increases the number of neural precursor cells (nestin-positive) around the lesion of ICH rats compared to hydrogel or EGF alone, with some of the cells differentiating to $TUJ1^+$ neurons; neurological recovery is better in the EGF-hydrogel group [112]. Self-assembling peptide nanofiber scaffolds (SAPNS) can eventually become hydrogels after delivery and promote wound healing [113].

RADA16-I is a type of SAPNS that after injection combined with hematoma aspiration improves functional recovery in experimental ICH but almost no neurons or nerve fibers were found in the matrix [114]; a modification was made to alter its acid property to neutral, which led to nerve fibers growing within and better behavioral performance [115]. Intravenous administration of ceria nanoparticles aids OPCs proliferation, maturation, and remyelination in the collagenase model; EdU^+CC1^+ (proliferated mature OLs) and $Oligo2^+CC1^+$ (mature OL lineage cell) cell counting is elevated at 7 days after injury compared to vehicle treatment, while MBP positive area and thickness of myelin sheath are increased at 21 days [116].

5. Rehabilitation Training

Rehabilitation has been widely used for decades to improve patients' functional recovery after ICH and shown stable efficacy [117][118]. Growing evidence from clinical trials and a cohort study suggest that rehabilitation should be implemented as early as possible and continue for a more extended period [119][120][121][122]. However, the method of post-ICH rehabilitation has followed the same pattern of ischemic stroke in clinical practice. The data from preclinical studies may give us inspiration for ICH specific rehabilitation. Skilled reach training requires animals to reach food through a narrow gap with one forelimb, which promotes astrocyte process growth, dendritic reorganization, and BDNF level, as well as improving sensorimotor functions in the collagenase induced ICH model [123][124]. An enriched environment contains tunnels, toys, and others to provide animals with multiple forms of sensory stimulation and more opportunities for physical activity, which not only improves functional recovery but also increases the dendritic length and reduces lesion volume and neuronal death after experimental ICH when combined with skilled reach training [125][126][127][128]. Acrobatic training provides a route that includes various types of barriers for mice to walk through repeatedly; motor function and coordinated movement ability are significantly restored after training in the collagenase model, and enhanced neuronal activity and synaptic remodeling are also observed [129]. Application of treadmill running, a type of aerobic training on post-ICH animals, induces longer dendritic length, complexity, and lower motor deficits [130]. Although some results suggest that rehabilitation may reduce lesion or cell death, most of the mechanisms elucidated in preclinical studies are related to neuronal or synaptic plasticity, partially attributed to astroglial activity. Recently, some innovative techniques of rehabilitation have emerged in clinical studies of ICH. Vagus nerve stimulation added to rehabilitative training prompts a much higher rate of functional recovery than patients of the rehabilitation-only group [131]. A clinical trial for robot-assisted therapy displays ameliorated neurological deficits of stroke (ICH included) patients compared with the non-physical trained group but not with patients accepted for intensive rehabilitation [132]. Nevertheless, more beneficial attempts

are encouraged and necessary to alleviate disability after ICH by exploring advanced technology and task designs that may be distinctive for hemorrhagic stroke due to different anatomical predilection and pathophysiology from ischemic stroke.

References

1. Cordonnier, C.; Demchuk, A.; Ziai, W.; Anderson, C.S. Intracerebral haemorrhage: Current approaches to acute management. Lancet 2018, 392, 1257–1268.
2. van Asch, C.J.; Luitse, M.J.; Rinkel, G.J.; van der Tweel, I.; Algra, A.; Klijn, C.J. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: A systematic review and meta-analysis. Lancet Neurol. 2010, 9, 167–176.
3. Kang, D.W. Intracerebral Hemorrhage: Large Disease Burden but Less Therapeutic Progress. J. Stroke 2017, 19, 1–2.
4. An, S.J.; Kim, T.J.; Yoon, B.W. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. J. Stroke 2017, 19, 3–10.
5. Xia, Z.; Wu, X.; Li, J.; Liu, Z.; Chen, F.; Zhang, L.; Zhang, H.; Wan, X.; Cheng, Q. Minimally Invasive Surgery is Superior to Conventional Craniotomy in Patients with Spontaneous Supratentorial Intracerebral Hemorrhage: A Systematic Review and Meta-Analysis. World Neurosurg. 2018, 115, 266–273.
6. Scaggiante, J.; Zhang, X.; Mocco, J.; Kellner, C.P. Minimally Invasive Surgery for Intracerebral Hemorrhage. Stroke 2018, 49, 2612–2620.
7. Hanley, D.F.; Thompson, R.E.; Rosenblum, M.; Yenokyan, G.; Lane, K.; McBee, N.; Mayo, S.W.; Bistran-Hall, A.J.; Gandhi, D.; Mould, W.A.; et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): A randomised, controlled, open-label, blinded endpoint phase 3 trial. Lancet 2019, 393, 1021–1032.
8. Xue, M.; Yong, V.W. Neuroinflammation in intracerebral haemorrhage: Immunotherapies with potential for translation. Lancet Neurol. 2020, 19, 1023–1032.
9. Chen, M.; Zheng, B. Axon plasticity in the mammalian central nervous system after injury. Trends Neurosci. 2014, 37, 583–593.
10. Emery, D.L.; Royo, N.C.; Fischer, I.; Saatman, K.E.; McIntosh, T.K. Plasticity following injury to the adult central nervous system: Is recapitulation of a developmental state worth promoting? J. Neurotrauma 2003, 20, 1271–1292.
11. Taupin, P. Adult neurogenesis and neuroplasticity. Restor. Neurol. Neurosci. 2006, 24, 9–15.

12. Stangel, M.; Kuhlmann, T.; Matthews, P.M.; Kilpatrick, T.J. Achievements and obstacles of remyelinating therapies in multiple sclerosis. Nat. Rev. Neurol. 2017, 13, 742–754.
13. Behrendt, G.; Baer, K.; Buffo, A.; Curtis, M.A.; Faull, R.L.; Rees, M.I.; Gotz, M.; Dimou, L. Dynamic changes in myelin aberrations and oligodendrocyte generation in chronic amyloidosis in mice and men. Glia 2013, 61, 273–286.
14. Wang, F.; Ren, S.Y.; Chen, J.F.; Liu, K.; Li, R.X.; Li, Z.F.; Hu, B.; Niu, J.Q.; Xiao, L.; Chan, J.R.; et al. Myelin degeneration and diminished myelin renewal contribute to age-related deficits in memory. Nat. Neurosci. 2020, 23, 481–486.
15. Uyeda, A.; Muramatsu, R. Molecular Mechanisms of Central Nervous System Axonal Regeneration and Remyelination: A Review. Int. J. Mol. Sci. 2020, 21, 8116.
16. Reuter, H.; Vogg, M.C.; Serras, F. Repair, regenerate and reconstruct: Meeting the state-of-the-art. Development 2019, 146, dev176974.
17. Ming, G.L.; Song, H. Adult neurogenesis in the mammalian central nervous system. Annu Rev. Neurosci. 2005, 28, 223–250.
18. Qureshi, A.I.; Mendelow, A.D.; Hanley, D.F. Intracerebral haemorrhage. Lancet 2009, 373, 1632–1644.
19. Powers, W.J.; Rabinstein, A.A.; Ackerson, T.; Adeoye, O.M.; Bambakidis, N.C.; Becker, K.; Biller, J.; Brown, M.; Demaerschalk, B.M.; Hoh, B.; et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019, 50, e344–e418.
20. Meschia, J.F.; Bushnell, C.; Boden-Albala, B.; Braun, L.T.; Bravata, D.M.; Chaturvedi, S.; Creager, M.A.; Eckel, R.H.; Elkind, M.S.; Fornage, M.; et al. Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014, 45, 3754–3832.
21. Amarenco, P.; Labreuche, J. Lipid management in the prevention of stroke: Review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. 2009, 8, 453–463.
22. Amarenco, P.; Bogousslavsky, J.; Callahan, A., 3rd; Goldstein, L.B.; Hennerici, M.; Rudolph, A.E.; Sillesen, H.; Simunovic, L.; Szarek, M.; Welch, K.M.; et al. High-dose atorvastatin after stroke or transient ischemic attack. N. Engl. J. Med. 2006, 355, 549–559.
23. McKinney, J.S.; Kostis, W.J. Statin therapy and the risk of intracerebral hemorrhage: A meta-analysis of 31 randomized controlled trials. Stroke 2012, 43, 2149–2156.
24. Ziff, O.J.; Banerjee, G.; Ambler, G.; Werring, D.J. Statins and the risk of intracerebral haemorrhage in patients with stroke: Systematic review and meta-analysis. J. Neurol. Neurosurg.

Psychiatry 2019, 90, 75–83.

25. Ribe, A.R.; Vestergaard, C.H.; Vestergaard, M.; Fenger-Gron, M.; Pedersen, H.S.; Lietzen, L.W.; Brynningsen, P.K. Statins and Risk of Intracerebral Haemorrhage in a Stroke-Free Population: A Nationwide Danish Propensity Score Matched Cohort Study. EClinicalMedicine 2019, 8, 78–84.
26. Tapia-Perez, H.; Sanchez-Aguilar, M.; Torres-Corzo, J.G.; Rodriguez-Leyva, I.; Gonzalez-Aguirre, D.; Gordillo-Moscoso, A.; Chalita-Williams, C. Use of statins for the treatment of spontaneous intracerebral hemorrhage: Results of a pilot study. Cent. Eur. Neurosurg. 2009, 70, 15–20.
27. Karki, K.; Knight, R.A.; Han, Y.; Yang, D.; Zhang, J.; Ledbetter, K.A.; Chopp, M.; Seyfried, D.M. Simvastatin and atorvastatin improve neurological outcome after experimental intracerebral hemorrhage. Stroke 2009, 40, 3384–3389.
28. Seyfried, D.; Han, Y.; Lu, D.; Chen, J.; Bydon, A.; Chopp, M. Improvement in neurological outcome after administration of atorvastatin following experimental intracerebral hemorrhage in rats. J. Neurosurg. 2004, 101, 104–107.
29. Yang, D.; Han, Y.; Zhang, J.; Chopp, M.; Seyfried, D.M. Statins Enhance Expression of Growth Factors and Activate the PI3K/Akt-mediated Signaling Pathway after Experimental Intracerebral Hemorrhage. World J. Neurosci 2012, 2, 74–80.
30. Yang, D.; Knight, R.A.; Han, Y.; Karki, K.; Zhang, J.; Ding, C.; Chopp, M.; Seyfried, D.M. Vascular recovery promoted by atorvastatin and simvastatin after experimental intracerebral hemorrhage: Magnetic resonance imaging and histological study. J. Neurosurg. 2011, 114, 1135–1142.
31. Wang, Y.; Chen, Q.; Tan, Q.; Feng, Z.; He, Z.; Tang, J.; Feng, H.; Zhu, G.; Chen, Z. Simvastatin accelerates hematoma resolution after intracerebral hemorrhage in a PPARgamma-dependent manner. Neuropharmacology 2018, 128, 244–254.
32. Wu, J.; Yang, S.; Xi, G.; Fu, G.; Keep, R.F.; Hua, Y. Minocycline reduces intracerebral hemorrhage-induced brain injury. Neurol. Res. 2009, 31, 183–188.
33. Yang, H.; Gao, X.J.; Li, Y.J.; Su, J.B.; E, T.Z.; Zhang, X.; Ni, W.; Gu, Y.X. Minocycline reduces intracerebral hemorrhage-induced white matter injury in piglets. CNS Neurosci. Ther. 2019, 25, 1195–1206.
34. Tikka, T.; Fiebich, B.L.; Goldsteins, G.; Keinanen, R.; Koistinaho, J. Minocycline, a tetracycline derivative, is neuroprotective against excitotoxicity by inhibiting activation and proliferation of microglia. J. Neurosci. 2001, 21, 2580–2588.
35. Kobayashi, K.; Imagama, S.; Ohgomori, T.; Hirano, K.; Uchimura, K.; Sakamoto, K.; Hirakawa, A.; Takeuchi, H.; Suzumura, A.; Ishiguro, N.; et al. Minocycline selectively inhibits M1 polarization of microglia. Cell Death Dis. 2013, 4, e525.

36. Sun, N.; Shen, Y.; Han, W.; Shi, K.; Wood, K.; Fu, Y.; Hao, J.; Liu, Q.; Sheth, K.N.; Huang, D.; et al. Selective Sphingosine-1-Phosphate Receptor 1 Modulation Attenuates Experimental Intracerebral Hemorrhage. Stroke 2016, 47, 1899–1906.
37. Pu, J.; Shi, W.; Wang, Z.; Wang, R.; Guo, Z.; Liu, C.; Sun, J.; Gao, L.; Zhou, R. Effects of minocycline on the expression of NGF and HSP70 and its neuroprotection role following intracerebral hemorrhage in rats. J. Biomed. Res. 2011, 25, 292–298.
38. Wang, R.; Hao, D.; Shi, W.; Pu, J.; Wang, Z. Effects of minocycline on apoptosis and angiogenesis-related protein expression in a rat model of intracerebral hemorrhage. Neural. Regen. Res. 2012, 7, 595–600.
39. Fouda, A.Y.; Newsome, A.S.; Spellicy, S.; Waller, J.L.; Zhi, W.; Hess, D.C.; Ergul, A.; Edwards, D.J.; Fagan, S.C.; Switzer, J.A. Minocycline in Acute Cerebral Hemorrhage: An Early Phase Randomized Trial. Stroke 2017, 48, 2885–2887.
40. Chang, J.J.; Kim-Tenser, M.; Emanuel, B.A.; Jones, G.M.; Chapple, K.; Alikhani, A.; Sanossian, N.; Mack, W.J.; Tsivgoulis, G.; Alexandrov, A.V.; et al. Minocycline and matrix metalloproteinase inhibition in acute intracerebral hemorrhage: A pilot study. Eur. J. Neurol. 2017, 24, 1384–1391.
41. O'Sullivan, S.; Dev, K.K. Sphingosine-1-phosphate receptor therapies: Advances in clinical trials for CNS-related diseases. Neuropharmacology 2017, 113, 597–607.
42. Noda, H.; Takeuchi, H.; Mizuno, T.; Suzumura, A. Fingolimod phosphate promotes the neuroprotective effects of microglia. J. Neuroimmunol. 2013, 256, 13–18.
43. Qin, C.; Fan, W.H.; Liu, Q.; Shang, K.; Murugan, M.; Wu, L.J.; Wang, W.; Tian, D.S. Fingolimod Protects Against Ischemic White Matter Damage by Modulating Microglia Toward M2 Polarization via STAT3 Pathway. Stroke 2017, 48, 3336–3346.
44. Yang, Z.; Dong, S.; Zheng, Q.; Zhang, L.; Tan, X.; Zou, J.; Yan, B.; Chen, Y. FTY720 attenuates iron deposition and glial responses in improving delayed lesion and long-term outcomes of collagenase-induced intracerebral hemorrhage. Brain Res. 2019, 1718, 91–102.
45. Tschoe, C.; Bushnell, C.D.; Duncan, P.W.; Alexander-Miller, M.A.; Wolfe, S.Q. Neuroinflammation after Intracerebral Hemorrhage and Potential Therapeutic Targets. J. Stroke 2020, 22, 29–46.
46. Li, Y.J.; Chang, G.Q.; Liu, Y.; Gong, Y.; Yang, C.; Wood, K.; Shi, F.D.; Fu, Y.; Yan, Y. Fingolimod alters inflammatory mediators and vascular permeability in intracerebral hemorrhage. Neurosci. Bull. 2015, 31, 755–762.
47. Rolland, W.B.; Lekic, T.; Krafft, P.R.; Hasegawa, Y.; Altay, O.; Hartman, R.; Ostrowski, R.; Manaenko, A.; Tang, J.; Zhang, J.H. Fingolimod reduces cerebral lymphocyte infiltration in experimental models of rodent intracerebral hemorrhage. Exp. Neurol. 2013, 241, 45–55.

48. Napier, J.; Rose, L.; Adeoye, O.; Hooker, E.; Walsh, K.B. Modulating acute neuroinflammation in intracerebral hemorrhage: The potential promise of currently approved medications for multiple sclerosis. Immunopharmacol. Immunotoxicol. 2019, 41, 7–15.

49. Fu, Y.; Hao, J.; Zhang, N.; Ren, L.; Sun, N.; Li, Y.J.; Yan, Y.; Huang, D.; Yu, C.; Shi, F.D. Fingolimod for the treatment of intracerebral hemorrhage: A 2-arm proof-of-concept study. JAMA Neurol. 2014, 71, 1092–1101.

50. Bobinger, T.; Manaenko, A.; Burkardt, P.; Beuscher, V.; Sprugel, M.I.; Roeder, S.S.; Bauerle, T.; Seyler, L.; Nagel, A.M.; Linker, R.A.; et al. Siponimod (BAF-312) Attenuates Perihemorrhagic Edema And Improves Survival in Experimental Intracerebral Hemorrhage. Stroke 2019, 50, 3246–3254.

51. Bobinger, T.; Bauerle, T.; Seyler, L.; v Horsten, S.; Schwab, S.; Huttner, H.B.; Manaenko, A. A Sphingosine-1-Phosphate Receptor Modulator Attenuated Secondary Brain Injury and Improved Neurological Functions of Mice after ICH. Oxid Med. Cell Longev. 2020, 2020, 3214350.

52. Baldessarini, R.J.; Tondo, L.; Davis, P.; Pompili, M.; Goodwin, F.K.; Hennen, J. Decreased risk of suicides and attempts during long-term lithium treatment: A meta-analytic review. Bipolar. Disord. 2006, 8, 625–639.

53. Li, R.; Liu, Z.; Wu, X.; Yu, Z.; Zhao, S.; Tang, X. Lithium chloride promoted hematoma resolution after intracerebral hemorrhage through GSK-3beta-mediated pathways-dependent microglia phagocytosis and M2-phenotype differentiation, angiogenesis and neurogenesis in a rat model. Brain Res. Bull. 2019, 152, 117–127.

54. Li, M.; Xia, M.; Chen, W.; Wang, J.; Yin, Y.; Guo, C.; Li, C.; Tang, X.; Zhao, H.; Tan, Q.; et al. Lithium treatment mitigates white matter injury after intracerebral hemorrhage through brain-derived neurotrophic factor signaling in mice. Transl. Res. 2020, 217, 61–74.

55. Ni, W.; Mao, S.; Xi, G.; Keep, R.F.; Hua, Y. Role of Erythrocyte CD47 in Intracerebral Hematoma Clearance. Stroke 2016, 47, 505–511.

56. Jing, C.; Bian, L.; Wang, M.; Keep, R.F.; Xi, G.; Hua, Y. Enhancement of Hematoma Clearance With CD47 Blocking Antibody in Experimental Intracerebral Hemorrhage. Stroke 2019, 50, 1539–1547.

57. Tao, C.; Keep, R.F.; Xi, G.; Hua, Y. CD47 Blocking Antibody Accelerates Hematoma Clearance After Intracerebral Hemorrhage in Aged Rats. Transl. Stroke Res. 2020, 11, 541–551.

58. Guan, J.; Zhang, B.; Zhang, J.; Ding, W.; Xiao, Z.; Zhu, Z.; Han, Q.; Wu, C.; Sun, Y.; Tong, W.; et al. Nerve regeneration and functional recovery by collagen-binding brain-derived neurotrophic factor in an intracerebral hemorrhage model. Tissue Eng. Part A 2015, 21, 62–74.

59. Han, Q.Q.; Jin, W.; Xiao, Z.F.; Huang, J.C.; Ni, H.B.; Kong, J.; Wu, J.; Chen, B.; Liang, W.B.; Dai, J.W. The promotion of neurological recovery in an intracerebral hemorrhage model using fibrin-

binding brain derived neurotrophic factor. Biomaterials 2011, 32, 3244–3252.

60. An, S.; Jia, Y.; Tian, Y.; Sun, J.; Wei, Y.; Yue, S.; Lin, L.; Wei, Y.; Li, Y.; Lei, P.; et al. Mouse nerve growth factor promotes neurological recovery in patients with acute intracerebral hemorrhage: A proof-of-concept study. J. Neurol. Sci. 2020, 418, 117069.
61. Chen, L.; Xi, H.; Huang, H.; Zhang, F.; Liu, Y.; Chen, D.; Xiao, J. Multiple cell transplantation based on an intraparenchymal approach for patients with chronic phase stroke. Cell Transplant. 2013, 22 (Suppl. 1), S83–S91.
62. Li, Z.M.; Zhang, Z.T.; Guo, C.J.; Geng, F.Y.; Qiang, F.; Wang, L.X. Autologous bone marrow mononuclear cell implantation for intracerebral hemorrhage-a prospective clinical observation. Clin. Neurol. Neurosurg. 2013, 115, 72–76.
63. Chang, Z.; Mao, G.; Sun, L.; Ao, Q.; Gu, Y.; Liu, Y. Cell therapy for cerebral hemorrhage: Five year follow-up report. Exp. Ther. Med. 2016, 12, 3535–3540.
64. Tsang, K.S.; Ng, C.P.S.; Zhu, X.L.; Wong, G.K.C.; Lu, G.; Ahuja, A.T.; Wong, K.S.L.; Ng, H.K.; Poon, W.S. Phase I/II randomized controlled trial of autologous bone marrow-derived mesenchymal stem cell therapy for chronic stroke. World J. Stem. Cells 2017, 9, 133–143.
65. Cordeiro, M.F.; Horn, A.P. Stem cell therapy in intracerebral hemorrhage rat model. World J. Stem. Cells 2015, 7, 618–629.
66. Marsh, S.E.; Blurton-Jones, M. Neural stem cell therapy for neurodegenerative disorders: The role of neurotrophic support. Neurochem. Int. 2017, 106, 94–100.
67. Gao, L.; Xu, W.; Li, T.; Chen, J.; Shao, A.; Yan, F.; Chen, G. Stem Cell Therapy: A Promising Therapeutic Method for Intracerebral Hemorrhage. Cell Transplant. 2018, 27, 1809–1824.
68. Hsu, Y.C.; Chen, S.L.; Wang, D.Y.; Chiu, I.M. Stem cell-based therapy in neural repair. Biomed. J. 2013, 36, 98–105.
69. Ryu, S.; Lee, S.H.; Kim, S.U.; Yoon, B.W. Human neural stem cells promote proliferation of endogenous neural stem cells and enhance angiogenesis in ischemic rat brain. Neural. Regen. Res. 2016, 11, 298–304.
70. Giusto, E.; Donega, M.; Cossetti, C.; Pluchino, S. Neuro-immune interactions of neural stem cell transplants: From animal disease models to human trials. Exp. Neurol. 2014, 260, 19–32.
71. Wu, K.; Zhang, R.; Lu, Y.; Wen, L.; Li, Y.; Duan, R.; Yao, Y.; Jia, Y. Lin28B regulates the fate of grafted mesenchymal stem cells and enhances their protective effects against Alzheimer’s disease by upregulating IGF-2. J. Cell Physiol. 2019, 234, 21860–21876.
72. Huang, A.P.; Hsu, Y.H.; Wu, M.S.; Tsai, H.H.; Su, C.Y.; Ling, T.Y.; Hsu, S.H.; Lai, D.M. Potential of stem cell therapy in intracerebral hemorrhage. Mol. Biol. Rep. 2020, 47, 4671–4680.

73. Bedini, G.; Bersano, A.; Zanier, E.R.; Pischiutta, F.; Parati, E.A. Mesenchymal Stem Cell Therapy in Intracerebral Haemorrhagic Stroke. Curr. Med. Chem. 2018, 25, 2176–2197.
74. Wang, S.P.; Wang, Z.H.; Peng, D.Y.; Li, S.M.; Wang, H.; Wang, X.H. Therapeutic effect of mesenchymal stem cells in rats with intracerebral hemorrhage: Reduced apoptosis and enhanced neuroprotection. Mol. Med. Rep. 2012, 6, 848–854.
75. Liang, H.; Yin, Y.; Lin, T.; Guan, D.; Ma, B.; Li, C.; Wang, Y.; Zhang, X. Transplantation of bone marrow stromal cells enhances nerve regeneration of the corticospinal tract and improves recovery of neurological functions in a collagenase-induced rat model of intracerebral hemorrhage. Mol. Cells 2013, 36, 17–24.
76. Ding, R.; Lin, C.; Wei, S.; Zhang, N.; Tang, L.; Lin, Y.; Chen, Z.; Xie, T.; Chen, X.; Feng, Y.; et al. Therapeutic Benefits of Mesenchymal Stromal Cells in a Rat Model of Hemoglobin-Induced Hypertensive Intracerebral Hemorrhage. Mol. Cells 2017, 40, 133–142.
77. Cui, J.; Cui, C.; Cui, Y.; Li, R.; Sheng, H.; Jiang, X.; Tian, Y.; Wang, K.; Gao, J. Bone Marrow Mesenchymal Stem Cell Transplantation Increases GAP-43 Expression via ERK1/2 and PI3K/Akt Pathways in Intracerebral Hemorrhage. Cell Physiol. Biochem. 2017, 42, 137–144.
78. Kobayashi, T.; Ahlenius, H.; Thored, P.; Kobayashi, R.; Kokaia, Z.; Lindvall, O. Intracerebral infusion of glial cell line-derived neurotrophic factor promotes striatal neurogenesis after stroke in adult rats. Stroke 2006, 37, 2361–2367.
79. Gill, S.S.; Patel, N.K.; Hotton, G.R.; O'Sullivan, K.; McCarter, R.; Bunnage, M.; Brooks, D.J.; Svendsen, C.N.; Heywood, P. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat. Med. 2003, 9, 589–595.
80. Xing, B.; Xin, T.; Zhao, L.; Hunter, R.L.; Chen, Y.; Bing, G. Glial cell line-derived neurotrophic factor protects midbrain dopaminergic neurons against lipopolysaccharide neurotoxicity. J. Neuroimmunol. 2010, 225, 43–51.
81. Deng, L.; Gao, X.; Fan, G.; Yang, C. Effects of GDNF-Transfected Marrow Stromal Cells on Rats with Intracerebral Hemorrhage. J. Stroke Cerebrovasc. Dis. 2019, 28, 2555–2562.
82. Wang, C.; Cao, J.; Duan, S.; Xu, R.; Yu, H.; Huo, X.; Qian, Y. Effect of MicroRNA-126a-3p on Bone Marrow Mesenchymal Stem Cells Repairing Blood-brain Barrier and Nerve Injury after Intracerebral Hemorrhage. J. Stroke Cerebrovasc. Dis. 2020, 29, 104748.
83. Kuroda, Y.; Kitada, M.; Wakao, S.; Nishikawa, K.; Tanimura, Y.; Makinoshima, H.; Goda, M.; Akashi, H.; Inutsuka, A.; Niwa, A.; et al. Unique multipotent cells in adult human mesenchymal cell populations. Proc. Natl. Acad. Sci. USA 2010, 107, 8639–8643.
84. Wakao, S.; Kuroda, Y.; Ogura, F.; Shigemoto, T.; Dezawa, M. Regenerative Effects of Mesenchymal Stem Cells: Contribution of Muse Cells, a Novel Pluripotent Stem Cell Type that Resides in Mesenchymal Cells. Cells 2012, 1, 1045–1060.

85. Cao, J.; Yang, Z.; Xiao, R.; Pan, B. Regenerative potential of pluripotent nontumorgenetic stem cells: Multilineage differentiating stress enduring cells (Muse cells). Regen. Ther. 2020, 15, 92–96.
86. Shimamura, N.; Kakuta, K.; Wang, L.; Naraoka, M.; Uchida, H.; Wakao, S.; Dezawa, M.; Ohkuma, H. Neuro-regeneration therapy using human Muse cells is highly effective in a mouse intracerebral hemorrhage model. Exp. Brain Res. 2017, 235, 565–572.
87. Kuramoto, Y.; Takagi, T.; Tatebayashi, K.; Beppu, M.; Doe, N.; Fujita, M.; Yoshimura, S. Intravenous administration of human adipose-derived stem cells ameliorates motor and cognitive function for intracerebral hemorrhage mouse model. Brain Res. 2019, 1711, 58–67.
88. Chen, J.; Tang, Y.X.; Liu, Y.M.; Chen, J.; Hu, X.Q.; Liu, N.; Wang, S.X.; Zhang, Y.; Zeng, W.G.; Ni, H.J.; et al. Transplantation of adipose-derived stem cells is associated with neural differentiation and functional improvement in a rat model of intracerebral hemorrhage. CNS Neurosci. Ther. 2012, 18, 847–854.
89. Zhang, Y.; Deng, H.; Hu, Y.; Pan, C.; Wu, G.; Li, Q.; Tang, Z. Adipose-derived mesenchymal stem cells stereotactic transplantation alleviate brain edema from intracerebral hemorrhage. J. Cell Biochem. 2019, 120, 14372–14382.
90. Re, D.B.; Przedborski, S. Fractalkine: Moving from chemotaxis to neuroprotection. Nat. Neurosci. 2006, 9, 859–861.
91. Miller, R.J.; Rostene, W.; Apartis, E.; Banisadr, G.; Biber, K.; Milligan, E.D.; White, F.A.; Zhang, J. Chemokine action in the nervous system. J. Neurosci. 2008, 28, 11792–11795.
92. Harrison, J.K.; Jiang, Y.; Chen, S.; Xia, Y.; Maciejewski, D.; McNamara, R.K.; Streit, W.J.; Salafranca, M.N.; Adhikari, S.; Thompson, D.A.; et al. Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1-expressing microglia. Proc. Natl. Acad. Sci. USA 1998, 95, 10896–10901.
93. Li, G.; Yu, H.; Liu, N.; Zhang, P.; Tang, Y.; Hu, Y.; Zhang, Y.; Pan, C.; Deng, H.; Wang, J.; et al. Overexpression of CX3CR1 in Adipose-Derived Stem Cells Promotes Cell Migration and Functional Recovery After Experimental Intracerebral Hemorrhage. Front. Neurosci. 2019, 13, 462.
94. Yang, D.; Han, Y.; Zhang, J.; Seyda, A.; Chopp, M.; Seyfried, D.M. Therapeutic effect of human umbilical tissue-derived cell treatment in rats with experimental intracerebral hemorrhage. Brain Res. 2012, 1444, 1–10.
95. Liu, A.M.; Lu, G.; Tsang, K.S.; Li, G.; Wu, Y.; Huang, Z.S.; Ng, H.K.; Kung, H.F.; Poon, W.S. Umbilical cord-derived mesenchymal stem cells with forced expression of hepatocyte growth factor enhance remyelination and functional recovery in a rat intracerebral hemorrhage model. Neurosurgery 2010, 67, 357–365.

96. Jeong, S.W.; Chu, K.; Jung, K.H.; Kim, S.U.; Kim, M.; Roh, J.K. Human neural stem cell transplantation promotes functional recovery in rats with experimental intracerebral hemorrhage. Stroke 2003, 34, 2258–2263.
97. Lee, H.J.; Kim, K.S.; Kim, E.J.; Choi, H.B.; Lee, K.H.; Park, I.H.; Ko, Y.; Jeong, S.W.; Kim, S.U. Brain transplantation of immortalized human neural stem cells promotes functional recovery in mouse intracerebral hemorrhage stroke model. Stem. Cells 2007, 25, 1204–1212.
98. Wang, Z.; Cui, C.; Li, Q.; Zhou, S.; Fu, J.; Wang, X.; Zhuge, Q. Intracerebral transplantation of foetal neural stem cells improves brain dysfunction induced by intracerebral haemorrhage stroke in mice. J. Cell Mol. Med. 2011, 15, 2624–2633.
99. Qin, J.; Ma, X.; Qi, H.; Song, B.; Wang, Y.; Wen, X.; Wang, Q.M.; Sun, S.; Li, Y.; Zhang, R.; et al. Transplantation of Induced Pluripotent Stem Cells Alleviates Cerebral Inflammation and Neural Damage in Hemorrhagic Stroke. PLoS ONE 2015, 10, e0129881.
100. Qin, J.; Song, B.; Zhang, H.; Wang, Y.; Wang, N.; Ji, Y.; Qi, J.; Chandra, A.; Yang, B.; Zhang, Y.; et al. Transplantation of human neuro-epithelial-like stem cells derived from induced pluripotent stem cells improves neurological function in rats with experimental intracerebral hemorrhage. Neurosci. Lett. 2013, 548, 95–100.
101. Yamanaka, S. Pluripotent Stem Cell-Based Cell Therapy-Promise and Challenges. Cell Stem. Cell 2020, 27, 523–531.
102. Branscome, H.; Paul, S.; Yin, D.; El-Hage, N.; Agbottah, E.T.; Zadeh, M.A.; Liotta, L.A.; Kashanchi, F. Use of Stem Cell Extracellular Vesicles as a “Holistic” Approach to CNS Repair. Front. Cell Dev. Biol. 2020, 8, 455.
103. Gorabi, A.M.; Kiaie, N.; Barreto, G.E.; Read, M.I.; Tafti, H.A.; Sahebkar, A. The Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes in Treatment of Neurodegenerative Diseases. Mol. Neurobiol. 2019, 56, 8157–8167.
104. Otero-Ortega, L.; Gomez de Frutos, M.C.; Laso-Garcia, F.; Rodriguez-Frutos, B.; Medina-Gutierrez, E.; Lopez, J.A.; Vazquez, J.; Diez-Tejedor, E.; Gutierrez-Fernandez, M. Exosomes promote restoration after an experimental animal model of intracerebral hemorrhage. J. Cereb. Blood Flow Metab. 2018, 38, 767–779.
105. Han, Y.; Seyfried, D.; Meng, Y.; Yang, D.; Schultz, L.; Chopp, M.; Seyfried, D. Multipotent mesenchymal stromal cell-derived exosomes improve functional recovery after experimental intracerebral hemorrhage in the rat. J. Neurosurg. 2018, 131, 290–300.
106. Duan, S.; Wang, F.; Cao, J.; Wang, C. Exosomes Derived from MicroRNA-146a-5p-Enriched Bone Marrow Mesenchymal Stem Cells Alleviate Intracerebral Hemorrhage by Inhibiting Neuronal Apoptosis and Microglial M1 Polarization. Drug Des. Devel. Ther. 2020, 14, 3143–3158.

107. Shen, H.; Yao, X.; Li, H.; Li, X.; Zhang, T.; Sun, Q.; Ji, C.; Chen, G. Role of Exosomes Derived from miR-133b Modified MSCs in an Experimental Rat Model of Intracerebral Hemorrhage. J. Mol. Neurosci. 2018, 64, 421–430.

108. Nih, L.R.; Carmichael, S.T.; Segura, T. Hydrogels for brain repair after stroke: An emerging treatment option. Curr. Opin. Biotechnol. 2016, 40, 155–163.

109. Nih, L.R.; Gojgini, S.; Carmichael, S.T.; Segura, T. Dual-function injectable angiogenic biomaterial for the repair of brain tissue following stroke. Nat. Mater. 2018, 17, 642–651.

110. Xu, J.; Duan, Z.; Qi, X.; Ou, Y.; Guo, X.; Zi, L.; Wei, Y.; Liu, H.; Ma, L.; Li, H.; et al. Injectable Gelatin Hydrogel Suppresses Inflammation and Enhances Functional Recovery in a Mouse Model of Intracerebral Hemorrhage. Front. Bioeng. Biotechnol. 2020, 8, 785.

111. Hu, Y.; Liu, N.; Zhang, P.; Pan, C.; Zhang, Y.; Tang, Y.; Deng, H.; Aimaiti, M.; Zhang, Y.; Zhou, H.; et al. Preclinical Studies of Stem Cell Transplantation in Intracerebral Hemorrhage: A Systemic Review and Meta-Analysis. Mol. Neurobiol. 2016, 53, 5269–5277.

112. Lim, T.C.; Mandeville, E.; Weng, D.; Wang, L.S.; Kurisawa, M.; Leite-Morris, K.; Selim, M.H.; Lo, E.H.; Spector, M. Hydrogel-Based Therapy for Brain Repair After Intracerebral Hemorrhage. Transl. Stroke Res. 2020, 11, 412–417.

113. Schneider, A.; Garlick, J.A.; Egles, C. Self-assembling peptide nanofiber scaffolds accelerate wound healing. PLoS ONE 2008, 3, e1410.

114. Sang, L.Y.; Liang, Y.X.; Li, Y.; Wong, W.M.; Tay, D.K.; So, K.F.; Ellis-Behnke, R.G.; Wu, W.; Cheung, R.T. A self-assembling nanomaterial reduces acute brain injury and enhances functional recovery in a rat model of intracerebral hemorrhage. Nanomedicine 2015, 11, 611–620.

115. Zhang, N.; Luo, Y.; He, L.; Zhou, L.; Wu, W. A self-assembly peptide nanofibrous scaffold reduces inflammatory response and promotes functional recovery in a mouse model of intracerebral hemorrhage. Nanomedicine 2016, 12, 1205–1217.

116. Zheng, J.; Lu, J.; Mei, S.; Wu, H.; Sun, Z.; Fang, Y.; Xu, S.; Wang, X.; Shi, L.; Xu, W.; et al. Ceria nanoparticles ameliorate white matter injury after intracerebral hemorrhage: Microglia-astrocyte involvement in remyelination. J. Neuroinflammation 2021, 18, 43.

117. Hemphill, J.C., 3rd; Greenberg, S.M.; Anderson, C.S.; Becker, K.; Bendok, B.R.; Cushman, M.; Fung, G.L.; Goldstein, J.N.; Macdonald, R.L.; Mitchell, P.H.; et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2015, 46, 2032–2060.

118. Shoamanesh Co-Chair, A.; Patrice Lindsay, M.; Castellucci, L.A.; Cayley, A.; Crowther, M.; de Wit, K.; English, S.W.; Hoosein, S.; Huynh, T.; Kelly, M.; et al. Canadian stroke best practice recommendations: Management of Spontaneous Intracerebral Hemorrhage, 7th Edition Update 2020. Int. J. Stroke 2021, 16, 321–341.

119. Yen, H.C.; Jeng, J.S.; Chen, W.S.; Pan, G.S.; Chuang Pt Bs, W.Y.; Lee, Y.Y.; Teng, T. Early Mobilization of Mild-Moderate Intracerebral Hemorrhage Patients in a Stroke Center: A Randomized Controlled Trial. Neurorehabil. Neural. Repair. 2020, 34, 72–81.
120. Bai, Y.; Hu, Y.; Wu, Y.; Zhu, Y.; He, Q.; Jiang, C.; Sun, L.; Fan, W. A prospective, randomized, single-blinded trial on the effect of early rehabilitation on daily activities and motor function of patients with hemorrhagic stroke. J. Clin. Neurosci. 2012, 19, 1376–1379.
121. Liu, N.; Cadilhac, D.A.; Andrew, N.E.; Zeng, L.; Li, Z.; Li, J.; Li, Y.; Yu, X.; Mi, B.; Li, Z.; et al. Randomized controlled trial of early rehabilitation after intracerebral hemorrhage stroke: Difference in outcomes within 6 months of stroke. Stroke 2014, 45, 3502–3507.
122. Sreekrishnan, A.; Leasure, A.C.; Shi, F.D.; Hwang, D.Y.; Schindler, J.L.; Petersen, N.H.; Gilmore, E.J.; Kamel, H.; Sansing, L.H.; Greer, D.M.; et al. Functional Improvement Among Intracerebral Hemorrhage (ICH) Survivors up to 12 Months Post-injury. Neurocrit. Care 2017, 27, 326–333.
123. Mestriner, R.G.; Pagnussat, A.S.; Boisserand, L.S.; Valentim, L.; Netto, C.A. Skilled reaching training promotes astroglial changes and facilitated sensorimotor recovery after collagenase-induced intracerebral hemorrhage. Exp. Neurol. 2011, 227, 53–61.
124. Santos, M.V.; Pagnussat, A.S.; Mestriner, R.G.; Netto, C.A. Motor Skill Training Promotes Sensorimotor Recovery and Increases Microtubule-Associated Protein-2 (MAP-2) Immunoreactivity in the Motor Cortex after Intracerebral Hemorrhage in the Rat. ISRN Neurol. 2013, 2013, 159184.
125. MacLellan, C.L.; Plummer, N.; Silasi, G.; Auriat, A.M.; Colbourne, F. Rehabilitation promotes recovery after whole blood-induced intracerebral hemorrhage in rats. Neurorehabil. Neural. Repair. 2011, 25, 477–483.
126. Auriat, A.M.; Colbourne, F. Delayed rehabilitation lessens brain injury and improves recovery after intracerebral hemorrhage in rats. Brain Res. 2009, 1251, 262–268.
127. Auriat, A.M.; Wowk, S.; Colbourne, F. Rehabilitation after intracerebral hemorrhage in rats improves recovery with enhanced dendritic complexity but no effect on cell proliferation. Behav. Brain Res. 2010, 214, 42–47.
128. 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, 395–404.
129. Tamakoshi, K.; Ishida, A.; Takamatsu, Y.; Hamakawa, M.; Nakashima, H.; Shimada, H.; Ishida, K. 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.
130. Takamatsu, Y.; Ishida, A.; Hamakawa, M.; Tamakoshi, K.; Jung, C.G.; Ishida, K. Treadmill running improves motor function and alters dendritic morphology in the striatum after collagenase-induced

intracerebral hemorrhage in rats. Brain Res. 2010, 1355, 165–173.

131. Hays, S.A.; Khodaparast, N.; Hulsey, D.R.; Ruiz, A.; Sloan, A.M.; Rennaker, R.L., 2nd; Kilgard, M.P. Vagus nerve stimulation during rehabilitative training improves functional recovery after intracerebral hemorrhage. Stroke 2014, 45, 3097–3100.

132. Lo, A.C.; Guarino, P.D.; Richards, L.G.; Haselkorn, J.K.; Wittenberg, G.F.; Federman, D.G.; Ringer, R.J.; Wagner, T.H.; Krebs, H.I.; Volpe, B.T.; et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N. Engl. J. Med. 2010, 362, 1772–1783.