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.

Keywords: 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.

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