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REVIEW

Stem cell therapy in intracerebral hemorrhage rat model

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Abstract

Intracerebral hemorrhage (ICH) is a very complex pathology, with many different not fully elucidated etiologies and prognostics. It is the most severe subtype of stroke, with high mortality and morbidity rates. Unfortunately, despite the numerous promising preclinical assays including neuroprotective, anti-hypertensive, and anti-inflammatory drugs, to this moment only symptomatic treatments are available, motivating the search for new alternatives. In this context, stem cell therapy emerged as a promising tool. However, more than a decade has passed, and there is still much to be learned not only about stem cells, but also about ICH itself, and how these two pieces come together. To date, rats have been the most widely used animal model in this research field, and there is much more to be learned from and about them. In this review, we first summarize ICH epidemiology, risk factors, and pathophysiology. We then present different methods utilized to induce ICH in rats, and examine how accurately they represent the human disease. Next, we discuss the different types of stem cells used in previous ICH studies, also taking into account the tested transplantation sites. Finally, we summarize what has been achieved in assays with stem cells in rat models of ICH, and point out some relevant issues where attention must be given in future efforts.

Key words: Cell therapy; Intracerebral hemorrhage; Preclinical assays; Rat; Stem cells

Core tip: In this review, we first summarize intracerebral hemorrhage (ICH) epidemiology, risk factors, and pathophysiology. We then present different methods utilized to induce ICH in rats, and examine how accurately they represent the human disease. Next, we discuss the different types of stem cells used in previous ICH studies, also taking into account the tested transplantation sites. Finally, we summarize what has been achieved in assays with stem cells in rat models of ICH, and point out some relevant issues where attention must be given in future efforts.

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INTRODUCTION

Marginal or no success was achieved from decades of research for therapeutic alternatives for intracerebral hemorrhage (ICH)[1,2]. Despite the numerous promising preclinical assays including neuroprotective, anti-hypertensive, and anti-inflammatory drugs, only symptomatic treatments are currently available[2,3], which motivates the search for new alternatives. In this context, cell therapy emerged as a promising tool[4-6]. However, more than a decade has passed, and there is still much to be learned not only about stem cells, but also about ICH itself, and how these two pieces come together. It is clear that achieving a more detailed knowledge of each involved element is crucial to obtain better results.

INTRACEREBRAL HEMORRHAGE: A SEVERE AND HETEROGENEOUS PATHOLOGY

Epidemiology

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide. In 2008, nearly 17.3 million people lost their lives because of CVDs (30% of all deaths); of these, 6.2 million (35.8%) were to cerebrovascular accidents[7], alternatively referred as stroke. Among CVDs, coronary artery disease is responsible for the highest mortality rate on a worldwide basis, followed by stroke[7]. However, stroke mortality rates surpass those of the coronary artery disease in some world regions, like East Asia, Africa, and South America[8].

There are two types of stroke: ischemic and hemorrhagic. This review will focus on nontraumatic ICH, which corresponds to spontaneous leakage of blood within the brain parenchyma or ventricular spaces[1]. ICH is the most lethal subtype of stroke, often causing immediate death[9]. Secondary brain injuries may lead to delayed fatality when death does not occur shortly after the onset. One-year and five-year survival are estimated to be around merely 46% and 29%, respectively[10]. Beyond that, surviving patients are usually left with many limitations in motor and cognitive functions. Overall, ICH is less frequent than its ischemic counterpart, but the proportion fluctuates depending on the ethnic and racial group. Among Chinese people, for example, ICH accounts for about 33% of stroke cases, *vs* 12% in white populations[11]. On the same hand, global incidence of ICH per 100000 person-years is estimated to be around 24.6, reaching 51.8 in Asian populations[12].

Risk factors

High blood pressure is the major risk factor for CVDs[13], particularly ICH[14,15]. As a matter of fact, it is estimated that about 50% of ICH cases are caused by chronic hypertension[1]. There is a well established liaison between regular consumption of alcoholic beverages and high blood pressure, being this effect independent of age, body mass, smoking habits and physical activity[16-18]. Hypertension and ICH incidence are also linked to other lifestyle-related risk factors, such as smoking[19,20], physical inactivity[21], and high dietary sodium and/or fat consumption[22,23]. About 20% of cases are due to amyloid angiopathy, being this the second cause of ICH[24]. Amyloid deposition incidence is primarily associated with increasing age[25-27], but genetic factors also play an important role[28]. Oral anticoagulant intake is other important risk factor, which not only increases ICH risk, but also has higher intrinsic death rates[29,30]. Other relevant risk factors are obesity, diabetes mellitus, high blood cholesterol and other lipids, brain tumors, aneurysms, cerebrovascular malformations, cavernous angiomas, and arteriovenous fistulae[23,31].

Pathophysiology

As previously stated, hemorrhagic events in brain parenchyma or ventricular spaces are included in ICH. Bleeding associated with chronic hypertension usually originates from microaneurysms near or at bifurcations of penetrating brain arterioles which emanate from basilar arteries or anterior, middle, or posterior cerebral arteries[1,32,33]. In most cases, intraventricular hemorrhage is a consequence of ICH, resulting from hematoma expansion to the ventricular space[1]. This phenomenon increases mortality in nearly five times[34]. In more rare occasions, hematoma may extend to the subarachnoid space[31]. Amyloid angiopathy associated ICH is commonly lobar, often extending into the subarachnoid space and ventricles[35]. Size and location of hematoma are determinant factors in the disease outcome[36]. For example, even though patients commonly experience continued bleeding or rebleeding[37], the latter phenomenon is more recurrent in amyloid angiopathy-derived ICH[38].

Initial injuries are consequent of mechanical disruption of adjacent brain tissue by physical compression due to hematoma formation[1,31,39]. Most hematoma enlargement occurs in the first hours following ictus, but this growth can extend for many hours[40,41]. Disruption of the blood-brain barrier implies in the formation of plasma-derived perihematomal edema[42], which grows rapidly in the first two or three days and reaches full extension about fourteen days after ICH onset[43,44]. Edema evolution can be described in three phases[45]. In the first few hours, hematoma expands and retracts as a result of coagulation, depositing serum molecules in the surrounding tissue. In two to three days, inflammatory mediators come off from circulation. In the third and last phase, erythrocytes suffer degradation, which culminates in hemoglobin toxicity. Thrombin and iron from erythrocytes play major roles in secondary injuries[9,46]. In fact, iron overload seems to be related to the formation

of the perihematomal zone[47]. This area surrounds the edema and includes viable but very vulnerable tissue[45].

CELL THERAPY IN INTRACEREBRAL HEMORRHAGE ANIMAL MODELS

Rat: The animal model of choice

Most of the present ICH pathophysiology knowledge derives from studies in animal models. After all, animals assays offer many research advantages, such as the possibility to work with homogeneous groups by the control of variables concerning the subjects (*e.g.*, age, weight, feeding, activity, genetics, *etc.*), and the ICH itself (*e.g.*, time and site of the injury onset and its intensity). Moreover, this kind of study permits various types of biological assays from surviving subjects at any stage of the pathology.

By far, the majority of ICH studies on animals are performed on rodents, mostly on rats. This choice is understandable, once rats are cheap and convenient to house, easy to manipulate, have a plethora of related products for the most diverse purposes, and have a well described anatomophysiology, which, overall, shares considerable similarities with humans in cerebrovascular parameters[48]. However, there are some important differences that should not be underestimated or neglected.

White matter paucity in rat brains limits the similarities with the human condition[32]. Human brain proportion of white/gray matter shares more similitude with that of porcines and primates, but both are incomparably more expensive and complicated to handle if compared to rats[49]. In addition, if compared to humans, rats also have anatomical disparities in brain perforating arteries, as well as anatomical and biochemical differences in the basal ganglia[50]. It is important to notice that both structures have fundamental involvement in ICH model, especially considering that the commonest experimentally induced ICH is intrastriatal. Actually, this fact is probably included among the reasons why ICH prognostic differs so much in some parameters between rats and humans (more on these matters in the next section). Thus, even though rodents provide advantages as experimental models, multiple species should be used for more trustworthy results[51]. Additionally, rats and mice are also different in many anatomophysiological aspects[52], and tests should not be limited to either of the two.

Intracerebral hemorrhage replication

Bacterial collagenase injection is the most widespread method to induce ICH in rats, followed by autologous blood injection (ABI). The latter is one of the earliest methods developed to replicate ICH in rats. In this model, blood is collected from a superficial vessel and is injected directly into the brain, usually in the striatum[53]. The application of this protocol should be limited to blood toxicity and edema formation studies, once very important aspects of ICH pathology are absent, like small vessel rupture and hematoma expansion[54]. Moreover, especially in rats, ABI implies in exaggerated inflammatory response as a consequence of hemoglobin crystallization[55].

Collagenases are enzymes that break collagen peptide bonds[56]. Consequently, intracerebral injection of bacterial collagenase leads to the breakdown of the basal lamina of blood vessels, establishing the leakage of blood within the brain[57]. Through this method, rebleeding is present and functional impairments are more long lasting than that of ABI model[57]. Also, application is simpler[49]. However, dissolution of endothelial basal lamina causes ICH in an unnatural manner[32].

Even though collagenase injection model mimics ICH with more success than ABI, both show relevant limitations[54]. As previously stated, the standard collagenase and blood site of injection is the striatum, which differs importantly from the human counterpart in biochemical and anatomical features[50]. In top of that, ICH is often not restricted to single anatomical regions in humans, while this is what is achieved with both models[58]. Lastly, but certainly not least, both models comprise intracerebral injections. Therefore, some significant ICH unrelated injuries must be done in order to access the target structures: animal scalp and periosteum must be cut open, a hole must be drilled in the skull, and most importantly, a needle must perforate all brain superjacent structures[59].

As tacit in the Pathophysiology section of this review, ICH is a disease with multiple etiologies, which directly affect the prognostic. More than that, the role played by the ICH causing factors is probably unrestricted to the way the pathology is going to have a start, but is also determinant how it is going to evolve[49]. For example, it is deductible that ICH disrupted by anticoagulant intake develops differently, as hematoma might probably include uncoagulated blood[60].

Even though ICH affects mostly humans with chronic hypertension and advanced age, preclinical studies are predominantly conducted using young and healthy animals. The absence of comorbidities presumably implies in unrealistic outcomes and weaker translational power. Aware of this limitation, many efforts have been made on the last years to develop and use models with characteristic risk factors. ICH related functional outcomes are known to be more severe and long lasting in older[61-63] and chronic hypertensive[64] rats. The latter develop spontaneous ICH with location and distribution consistent to what is observed in hypertensive humans[32]. However, spontaneous chronic hypertension-derived ICH is hard to model, once animals tend to develop ischemic stroke instead of ICH[65].

Prognostic analysis of experimentally induced ICH

ICH in rats and humans have remarkably different prognostics. Human ICH is generally followed by

important long lasting or permanent cognitive and motor impairments. In contrast, rats subjected to ICH exhibit no (or at least not long lasting) cognitive deficits[58,66]. Brain structural disparities might play a crucial role in this matter, implying in different affected structures[58]. Motor function impairments in rats are present and well described, but undergo notable recovery in few weeks[67]. Moreover, in rats, edema reaches full extension three to four days after ICH onset[68], whereas in humans it takes weeks[69]. Although there is much to be discovered in this matter, rat superior neurogenesis and/or neuroplasticity may explain these dissimilarities[70].

Many behavioral tests are used to assess ICH outcome. Among the most used are the modified limb placement test (mLPT)[71] and the modified neurological severity score (mNSS)[72]. In both tests, rats are subjected to a set of simple sensorimotor tasks that evaluate different aspects of neurological function. A score is attributed to the performance in each task, resulting in a final sum that ranges from 0 to 14. Both mLPT and mNSS are theoretically consistent, simple to perform, and cost-free, dismissing the need for complex training and special equipments. However, both tests should be always applied by blinded investigators, preferably the same ones for every session. If such attention is present, it is commonly unknown, as it is not always mentioned. Evaluating rat behaviors through mLPT and mNSS can be considerably subjective and interpretative tasks, relying strongly on the observer sensitivity and judging parameters. Importantly, the small score amplitude (0-2 in mLPT and 0-1 in mNSS) attributed to each parameter may lead to significant variations in the final result. Thus, expectations of any nature and level should be absent in the assigned investigator for trustworthy results. Additionally, more than one single test should be applied for more solid assertions.

Last but not least, pathophysiological features of ischemic and hemorrhagic stroke diverge in many ways[73]. Thus, great caution should be taken when comparing findings from each disease.

Stem cell types and clinical applications: An ever-emerging science

Stem cells are characterized by ability of self-renewal (production of identical copies of themselves) and capability to differentiate into distinct functional cells. Cells with capability to differentiate into any body cell are called totipotent. These cells are only found in the earliest stages following fertilization. Embryonic stem cells (ESCs) are mostly pluripotent, meaning that they are able to maturate into cells of the three germ layers (endoderm, mesoderm, and ectoderm). Unfortunately, ESCs are very difficult to isolate, and their use is very limited and even avoided due to ethical, social and religious concerns[74]. Induced pluripotent stem cells (iPSCs) were developed to work around ESCs major issues. iPSCs are generated from somatic cells reprogrammed by the introduction of few defined factors[75]. However, as embryonic stem cells, iPSCs can potentially generate teratomas after transplantation[76-78]. It happens as a result of their propensity for uncontrolled self-renewal and triploblastic differentiation[79].

Somatic stem cells are multipotent, thus possessing the ability to differentiate into only certain cell types. As they can be found in adult tissues, they are sometimes referred as "adult stem cells". This term, however, is misleading and should be avoided, once the embryo starts containing somatic stem cells shortly after implantation[80]. Mesenchymal stem cells (MSCs) are somatic stem cells present in virtually all organs[81]. They are able to differentiate into mesodermal cell lineages, like osteoblasts, chondrocytes, adipocytes, and myoblasts[82,83]. Some groups, however, showed that MSCs can be induced to differentiate into neurons, but is debatable if they are functional[84]. Bone marrow and adipose tissue have been the preferred sources for MSCs, and cells from each origin are biologically different[82,85]. Bone marrow-derived stem cells (BMSCs) were the first to be discovered, and are the most tested in preclinical assays. However, if compared to BMSCs, adipose-derived stem cells (ASCs) are simpler and less invasive to harvest, as large amounts of these cells can be obtained *via* liposuction with local anesthesia only[86,87]. If ASC allogeneic applications become someday proven to be safe, fat from liposuctions can be utilized for stem cell cultures instead of being discarded. Moreover, adipose tissue yields more stem cells than any other source[88]. For example, ASCs are more frequent in adipose tissue than BMSCs are in bone marrow in a 100 to 500 fold difference[86]. Although considered very promising[89,90], ASC use is relatively recent if compared to BMSCs. Thus, more studies are needed in order to effectively evaluate advantages of one over another on particular purposes, concerning efficacy, safety, *etc*. Neural stem cells (NSCs) are multipotent and can differentiate into neurons, astrocytes, and oligodendrocytes. Even though NSCs might initially sound as the most appropriate for nervous system diseases like ICH, the isolation of these cells is a complicated and delicate procedure[91].

Umbilical cord-derived stem cells (UCSCs) are the most used cells from perinatal tissues. Controversy still exists if UCSCs are MSCs or MSC precursors, as they differ in morphological and behavioral aspects[83]. UCSCs are harvested from umbilical cord or umbilical cord blood (UCB) from newborns[92,93], which are presently treated as medical waste. Thus, the isolation method completely avoids donor morbidity[94]. UCSCs are very abundant and show high proliferative capacity[94,95]. UCB contains mononuclear cells that are mostly leucocytes, but it also contains UCSCs. Importantly, 0.6% of umbilical cord blood mononuclear cells are multipotent stress-enduring (Muse) cells. Muse cells are a non teratogenic pluripotent cell type that was recently isolated not only from UCB, but also from dermal fibroblasts, bone marrow, and adipose tissue[79,96,97].

Autologous stem cell transplantation guarantees the absence of immune rejection. However, depending on the circumstances, this might not be feasible. For instance, somatic stem cells require several weeks in culture to achieve sufficient proliferation[91]. Additionally, the harvested cells themselves may not be appropriate in number and/or quality for therapeutic purposes (*e.g.*, in case of elder patients). More than that, harvesting might be a painful and complicated procedure to the patient (*e.g.*, BMSCs). Cells from perinatal tissues could be used for autologous administration, but this practice would be very resource demanding, comprising long term storage of the isolated cells in freezers until they are eventually needed[98].

It is not consensual if allogeneic delivery of MSCs would lead to immune rejection. Actually, many findings with somatic stem cells showed that they possess immunossupressive action, not being rejected by the host organism[99-102]. If lack of immune rejection becomes confirmed for allogeneic somatic stem cell transplants, this would certainly represent the preferred option, making it possible that cultured cells are readily available for the patients. ESCs, by the other hand, are known to trigger immune responses following allogeneic transplantation. Taking that into consideration, research is being conducted in order to inhibit donor-host immune reactions[103].

Stem cell therapeutic effects and underlying mechanisms

It was in the beginning of the last decade that stem cells started to be considered as a treatment for neurological disorders. Back then, the expected therapeutic mechanism was very simple: stem cells were expected to repopulate the damaged tissue, differentiating into functional neurons and glial cells[104,105]. Actually, a considerable number of earlier studies have mistakenly concluded that MSCs and UCBCs could in fact differentiate into functional mature neurons and astrocytes, but these findings were contested[84,106]. NSCs are the only type of somatic stem cell capable to differentiate into functional mature nervous cells. But again, probably it is not the main action underlying NSC therapeutic effects. The underlying mechanisms are presently recognized to be far more complex, and are still not fully understood.

Evidence show that therapeutic effects primarily emerge from the release of trophic factors, cytokines, and microRNAs that stimulate endogenous mechanisms of repair[106-109]. In consonance with this, in a recent work, Jeon *et al*[110] reported a modest, yet significant recovery in rats subjected to ICH treated only with ASC extract. Additionally, different research groups already reported that endogenous NSCs are stimulated and recruited to the injury site in response to exogenous stem cell injection[111,112]. In fact, the injury itself seems to stimulate stem cells, exogenous and endogenous, to migrate to the perihematoma perimeter[113-117] and to promote proliferation and plasticity[108,111,118,119]. These restorative reactions are probably consequent of the secretion of trophic factors, which is the most likely mechanism underlying apoptosis prevention as well[111,113,119-121]. The same is true to the intensified angiogenesis, presumably due to elevated VEGF release[66,113,122,123]. Hematoma area reduction is also often observed[66,115,119,121,124], but not always[112-114,117]. Likewise, decrement of brain edema volume is a commonly stated benefice[113,125,126]. Stem cells are also seen to exert important anti-inflammatory effects in the injury site[66,113,125,126], being known to modulate the action of dendritic cells, and B and T lymphocytes[127-129]. Stem cells were linked to astrocyte and microglia response modulation as well[130]. In fact, recent findings showed that some glial cells within the oligodendrocytic and astrocytic lineages present progenitor and neural stem cell functions, with active response to brain injury[131,132].

Preclinical studies: an heterogeneous approach for an heterogeneous disease

Present available data concerning stem cell therapy for ICH derives from investigations conducted with notably different approaches. Many stem cell administration routes have been tested, but it remains unclear which is the best option. Findings in ICH model support that cervical vein delivery is inefficient[133], whereas good outcomes were already observed following stem cell delivery in brain parenchyma[66,111,113-116,121,126,134-137], lateral ventricle[120,133], tail vein[117,119,122,124-126,138,139], and carotid artery[133,140,141]. However, each one of these alternatives has drawbacks. Intracerebral and intracerebroventricular routes are very invasive alternatives, hardly representing the best clinical options. In this sense, intravascular injections are incomparably more feasible and less troublesome, and allows injections with higher cell doses[142]. However, due to their size, stem cells were reported to get trapped in the lungs, liver and spleen and to cause embolisms, following tail vein and intracarotid injections, respectively[143-145]. Importantly, the latter adversity can be surpassed with slower injection rates[143], a generally overlooked variable. It was reported that carotid artery delivery favors cell migration to the brain if compared to tail vein delivery route[146]. However, no differences in this aspect were seen when comparing carotid artery and jugular vein stem cell injections[147]. Additionally, concerning intravascular transplantation, the potential of other systemic interactions is of unknown impact, being the safety of this route debatable.

Recently, efforts have been devoted to the development of new cell administration routes. Among these, intranasal cell delivery represents a promising alternative for the treatment of neurological disorders. Not only intranasal administration is simple and noninvasive, but also avoids potentially dangerous systemic interactions[148-151]. Positive results were reported following the delivery of growth factors[152-154] and MSCs[155-158] following experimentally-induced ischemic stroke in rodents. To our knowledge to

Table 1 Methodologies used in preclinical trials of stem cell therapy for intracerebral hemorrhage

Ref.	ICH model	Cells	Time after ICH	Amount	Vol (μL)	Delivery site
Bao *et al*[113]	Col Ⅶ	hBMSC (Flk-1+)	24 h	2×10^5	15	BP
Chen *et al*[120]	Col Ⅳ	ASC	48 h	3×10^6	10	LV
Fatar *et al*[112]	Col Ⅳ	hASC	24 h	3×10^6	500	TV
Jeon *et al*[110]	Col Ⅶ	ASC extract	1 h	-	-	IP
Jeong *et al*[138]	Col Ⅳ	hNSC	24 h	5×10^6	500	TV
Kim *et al*[125]	Col Ⅶ	hASC	24 h	3×10^6	2000	TV
Lee *et al*[126]	Col Ⅶ	hNSC	2 h; 24 h	5×10^6 (TV); 1×10^6 (IC)	500 (TV); 2 (BP)	TV; BP
Li *et al*[139]	Col Ⅶ	NSC	2 h; 7 h; 14 h; 21 h; 27 h	4×10^6	400	CA
Liang *et al*[114]	Col Ⅳ	BMSC	24 h	1×10^6	10	BP
Liao *et al*[66]	Col Ⅶ	hUCSC	24 h	2×10^5	10	BP
Nan *et al*[158]	Col Ⅶ	hUCB	24 h	2.4×10^6-3.2×10^6	500	SV
Otero *et al*[134]	Col Ⅳ	BMSC	72 h	2×10^6	10	BP
Otero *et al*[115]	Col Ⅳ	BMSC	2 m	5×10^6	15	BP
Otero *et al*[111]	Col Ⅳ	BMSC	2 h	2×10^6	15	BP
Qin *et al*[116]	Col Ⅶ	iPSC	24 h	2×10^6	10	BP
Qin *et al*[135]	Col Ⅶ	iPSC	24 h	1×10^6	10	BP
Seghatoleslam *et al*[124]	Col Ⅳ	hUCBMC	24 h	4×10^6; 8×10^6; 16×10^6	1000	TV
Seyfried *et al*[140]	ABI	BMSC	24 h	1×10^6	100	CA
Seyfried *et al*[122]	ABI	BMSC	24 h	5×10^5; 1×10^6	1000; 2000	TV
Vaquero *et al*[136]	Col Ⅳ	hBMSC[1]	2 m	5×10^6	30	BP
Wang *et al*[119]	Col Ⅶ	BMSC	1 h	1×10^6	1000	TV
Wang *et al*[137]	Col Ⅶ	NSC	72 h	1×10^6	500 (TV); 2 (BP)	TV; BP
Yang *et al*[121]	Col Ⅰ	BMSC (overexpressing GDNF)	72 h	5×10^5	20	BP
Yang *et al*[117]	ABI	hUCSC	24 h; 72 h; 7 d	3×10^6	2000	TV
Yang *et al*[159]	Col Ⅶ	hASC	24 h	1×10^6	200	FV
Zhang *et al*[133]	Col Ⅶ	BMSC	24 h; 72 h; 5 d; 7 d	2×10^6	20	CA; CV; LV

[1]Delivered in platelet-rich plasma scaffolds. Intracerebral hemorrhage (ICH) model: autologous blood injection (ABI) and collagenase (Col). Cell type: ASC: Adipose-derived stem cell; BMSC: Bone marrow-derived stem cell; GDNF: Glial-derived neurotrophic factor; iPSC: Induced pluripotent stem cell; UCB: Umbilical cord blood; UCBMC: Umbilical cord blood mononuclear cell; UCSC: Umbilical cord-derived stem cell; NSC: Neural stem cell. Delivery site: BP: Brain parenchyma; CA: Carotid artery; CV: Cervical vein; FV: Femoral vein; LV: Lateral ventricle; SV: Saphenous vein; TV: Tail vein.

date, no intranasal delivery trials were conducted on the treatment of ICH using MSCs.

Some comparative studies using different routes have been made on ischemic stroke models. Findings comparing cell migration and possible systemic adversities resulting from different stem cell injection routes represent potential lessons to apply in future ICH model investigations.

Stem cells have been delivered at many different times after experimental ICH onset, ranging from one hour to two months following ictus (Table 1). Apparently, earlier NSC transplantation (acute phase) is particularly important in intravenous delivery[126]. Interestingly, in the same study, time matter seemed to be indifferent when stem cell injection was intracerebral. Also working with NSCs, other group tested the effects of different carotid artery injection times. Acute phase delivery, in this case, returned the worst therapeutic effects[140]. In late transplantation studies, intracerebral stem cell implantation was performed only two months after ictus. Even so, good functional and morphological outcomes could be observed[111,136]. It is also important to keep in mind that ICH dynamics in rats and humans, as previously discussed, are clearly different in many aspects, including temporality. Thus, time windows in these different organisms are proportionally divergent, *e.g.*, 24 h after ICH onset, rodents and humans suffer from different pathological actions, due to the different paces in the development of the pathology.

The ideal amount of cells and vehicle to be injected is another unanswered question. The only studies performed with variations in that parameters used the tail vein route[122,122,124]. BMSC injection of 1 million cells was more therapeutically effective than half of it[122,122]. UCMCs were also more effective in the highest tested amount (16 million cells), reducing injury area with more success[124]. However, apart from this studies, the most common quantity injected in the tail vein is of 3 million cells, suspended in 1 or 2 mL of saline solution[117,119,124,125]. The amount of intracerebrally grafted cells varied up to 25 fold among studies[66,113,115,121,136]. Interestingly, in general, the vehicle volume is not necessarily proportional with the number of cells in suspension (Table 1).

Most of the aforementioned findings, however, are very hard to counterweigh and take as conclusive. Not only the time window after ICH varied between studies, but also the cell type, amount, and injection site. Moreover, it must be never forgotten that rats and humans are different organisms, and studies in more models must be performed before calculating the extrapolation to human applications. As stated in previous sections, different stem cell types have different attributes, and knowledge is in its youth about how all these divergences may affect ICH outcome.

CONCLUSION

In this review, we highlighted that there is still much to be learned about ICH and stem cells, both individually as interacting with each other. The approaches adopted by different groups were diverse, concerning not only the outcome evaluation, but also ICH induction and stem cell treatment protocols. Although it is important to perform tests under diverse conditions, more comparative studies should be motivated, including different times for interventions, stem cell types, quantities, and delivery sites. Homogeneity of all implicated variables except the one to be tested is imperative for the improvement of our understanding, preventing waste of hopes and resources in forthcoming human ICH trials.

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