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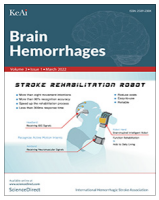

Review article

Stromal vascular fraction cell therapy: A promising therapeutic method for intracerebral hemorrhage

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ABSTRACT

Intracerebral hemorrhage (ICH) is one of the most devastating and life-threatening forms of stroke, characterized by bleeding within the brain parenchyma. The condition is associated with a high mortality rate and significant long-term disabilities among survivors, underscoring the urgent need for innovative therapeutic strategies that go beyond managing symptoms to actively promote brain repair and functional recovery. Current treatment options are largely limited to supportive care, including surgical interventions to alleviate intracranial pressure and management of underlying risk factors such as hypertension. These approaches, however, fail to address the extensive neurological damage caused by ICH. Emerging evidence highlights the potential of stromal vascular fraction (SVF) cell therapy as a novel regenerative treatment for ICH. SVF, derived from adipose tissue through enzymatic digestion, is a heterogeneous mixture of cells, including mesenchymal stem cells (MSCs), endothelial cells, pericytes, immune cells, and progenitor cells. This cellular composition contributes synergistically to the repair and regeneration of damaged tissues. The mechanisms of action of SVF encompass inflammation modulation, neuroprotection, angiogenesis, and immunomodulation. MSCs within SVF release anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), reducing secondary injury caused by excessive inflammation. Endothelial cells and pericytes promote the formation of new blood vessels, restoring oxygen and nutrient supply to ischemic regions. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) further support neuronal survival and repair of neural circuits. Preclinical studies in animal models have consistently demonstrated the efficacy of SVF therapy, including reductions in brain edema, oxidative stress, and inflammatory cytokines, alongside improvements in angiogenesis, neuronal survival, and functional recovery. Early-phase clinical trials and case studies provide preliminary evidence of safety, feasibility, and potential therapeutic benefits in human patients with acute and chronic ICH. However, significant challenges remain, including the variability in SVF composition, optimal delivery methods, timing of intervention, and long-term safety considerations. This review comprehensively examines the biological properties of SVF, the mechanisms underlying its therapeutic effects, and the preclinical and clinical evidence supporting its use in ICH. Additionally, it explores future directions, including the development of standardized protocols, optimization of delivery techniques, integration with combination therapies, and the potential for personalized medicine approaches. As ongoing research and clinical trials refine these strategies, SVF therapy holds transformative potential to revolutionize ICH treatment by addressing its complex pathophysiology and improving patient outcomes. This novel approach not only promises to mitigate the immediate impacts of ICH but also offers hope for long-term recovery and enhanced quality of life for affected individuals.

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1. Introduction

Intracerebral hemorrhage (ICH) is one of the most devastating forms of stroke, characterized by the sudden rupture of a blood vessel within the brain, leading to the accumulation of blood within the brain parenchyma.[1–2] This condition is associated with a high mortality rate, with approximately 40 % of patients succumbing to the condition within the first 30 days. Among those who survive, many are left with significant long-term disabilities that severely impact their quality of life.[3] The pathophysiology of ICH is complex, involving increased intracranial pressure, widespread inflammation, and extensive neurological damage. These factors contribute to the rapid deterioration of brain function, often resulting in severe cognitive and motor deficits. Current therapeutic approaches for ICH are primarily focused on supportive care, which includes measures to stabilize the patient and manage symptoms.[4–5] Surgical interventions, such as hematoma evacuation, are sometimes employed to reduce intracranial pressure, but these procedures carry significant risks and are not always feasible. In addition, the management of underlying risk factors, such as hypertension, is crucial in preventing the recurrence of hemorrhage. Despite these efforts, no existing treatments have been able to effectively reverse the brain damage caused by the hemorrhage or promote substantial recovery of neurological function.[6] This has led to an urgent need for novel therapeutic strategies that can address the underlying damage and improve outcomes for patients with ICH. In recent years, advances in regenerative medicine have opened new possibilities for treating neurological disorders, including stroke.[7] Regenerative medicine aims to repair or replace damaged tissues and organs, often using stem cells or other biologically active molecules. Among the various approaches being explored, stromal vascular fraction (SVF) therapy has emerged as a particularly promising candidate for the treatment of ICH.[8] SVF is derived from adipose tissue, which is a rich and accessible source of regenerative cells. The SVF is composed of a heterogeneous mixture of cells, including MSCs or adipose-derived stem cells (ADSCs), endothelial cells (ECs), pericytes, hematopoietic stem cells (HSCs), and various immune cells.[9] Each of these cell types plays a critical role in the processes of tissue repair, angiogenesis (the formation of new blood vessels), and immunomodulation. The potential of SVF to promote brain repair and functional recovery following ICH has garnered significant interest in the scientific and medical communities. SVF's diverse cellular composition allows it to address multiple aspects of the injury and recovery process simultaneously.[10] For instance, MSCs within the SVF can differentiate into various cell types and secrete factors that promote tissue repair and reduce inflammation. ECs contribute to the restoration of blood supply to the injured area by promoting angiogenesis, while pericytes support the integrity of newly formed blood vessels. Immune cells within the SVF can modulate the inflammatory response, potentially reducing secondary injury caused by excessive inflammation.[11]

This article aims to provide a comprehensive review of the current understanding of SVF cell therapy in the context of ICH treatment. We will explore the biological properties of SVF, including the specific roles of its various cellular components. Additionally, we will examine the mechanisms through which SVF exerts its therapeutic effects, such as its ability to reduce inflammation, protect neurons from further damage, and promote the repair of damaged brain tissue. The review will also discuss the existing preclinical and clinical evidence supporting the use of SVF therapy for ICH, highlighting both the successes and the challenges encountered thus far. Moreover, we will address the challenges associated with the clinical translation of SVF therapy, including issues related to the heterogeneity of the SVF cell population, the optimal methods for delivering SVF to the brain, and the timing of therapy relative to the onset of hemorrhage. Finally, we will explore potential future directions for SVF research, such as the development of combination therapies that could enhance the efficacy of SVF treatment and the establishment of standardized protocols to ensure the safety and consistency of SVF products. In summary, SVF therapy represents a novel and potentially transformative approach to the treatment of ICH. By harnessing the regenerative potential of adipose-derived cells, SVF therapy has the potential to address the critical unmet need for effective treatments that can not only manage the symptoms of ICH but also promote true recovery of brain function. With ongoing research and clinical trials, SVF therapy may soon offer new hope to patients suffering from this life-threatening condition.

2. Biological properties of SVF

2.1. Composition of SVF

SVF is obtained from the lipoaspirate of adipose tissue, which is a readily available and abundant source of regenerative cells. The process of isolating SVF involves the enzymatic digestion of adipose tissue, followed by centrifugation to separate the SVF from mature adipocytes.[12–14] The resulting cell population is highly heterogeneous, comprising various cell types that contribute to its therapeutic potential (Fig. 1).[12] MSCs – multipotent stem cells can differentiate into various mesodermal lineages, including adipocytes, osteocytes, and chondrocytes. MSCs are known for their immunomodulatory and anti-inflammatory properties, which are crucial for reducing secondary injury in the brain following ICH. ECs – form the inner lining of blood vessels and are essential for angiogenesis and vascular repair.[13] The presence of ECs in SVF contributes to the promotion of neovascularization in ischemic or damaged brain tissue. Pericytes – contractile cells wrap around ECs in capillaries and venules, providing structural support and contributing to the blood–brain barrier's (BBB) integrity.[13] Pericytes also have regenerative potential and can differentiate into MSCs. HSCs are multipotent stem cells that give rise to all blood cell types, including immune cells.[13] These cells play a role in modulating the immune response and promoting tissue repair. The SVF contains a variety of immune cells, such as macrophages, T cells, and B cells, which are involved in regulating inflammation and immune responses.[14] The balance between pro-inflammatory and anti-inflammatory immune cells within SVF is critical for its therapeutic efficacy. SVF also contains various progenitor cells, such as ADSCs and endothelial progenitor cells (EPCs), which contribute to tissue regeneration and repair.[14]

The diverse cell types within SVF interact synergistically to promote tissue repair, reduce inflammation, and enhance neuroprotection, making SVF a promising candidate for cell-based therapy in ICH.

2.2. Mechanisms of action

The therapeutic potential of SVF in treating ICH is underpinned by a variety of mechanisms that target the multifaceted nature of secondary brain injury following hemorrhagic stroke. Inflammation is a critical contributor to secondary brain damage after an ICH event, where the initial bleeding triggers a cascade of inflammatory responses that exacerbate brain injury.[15] SVF cells, particularly MSCs, play a pivotal role in modulating this inflammatory response. These cells secrete a range of anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). IL-10 is known for its ability to suppress the activity of pro-inflammatory cytokines, thereby limiting the extent

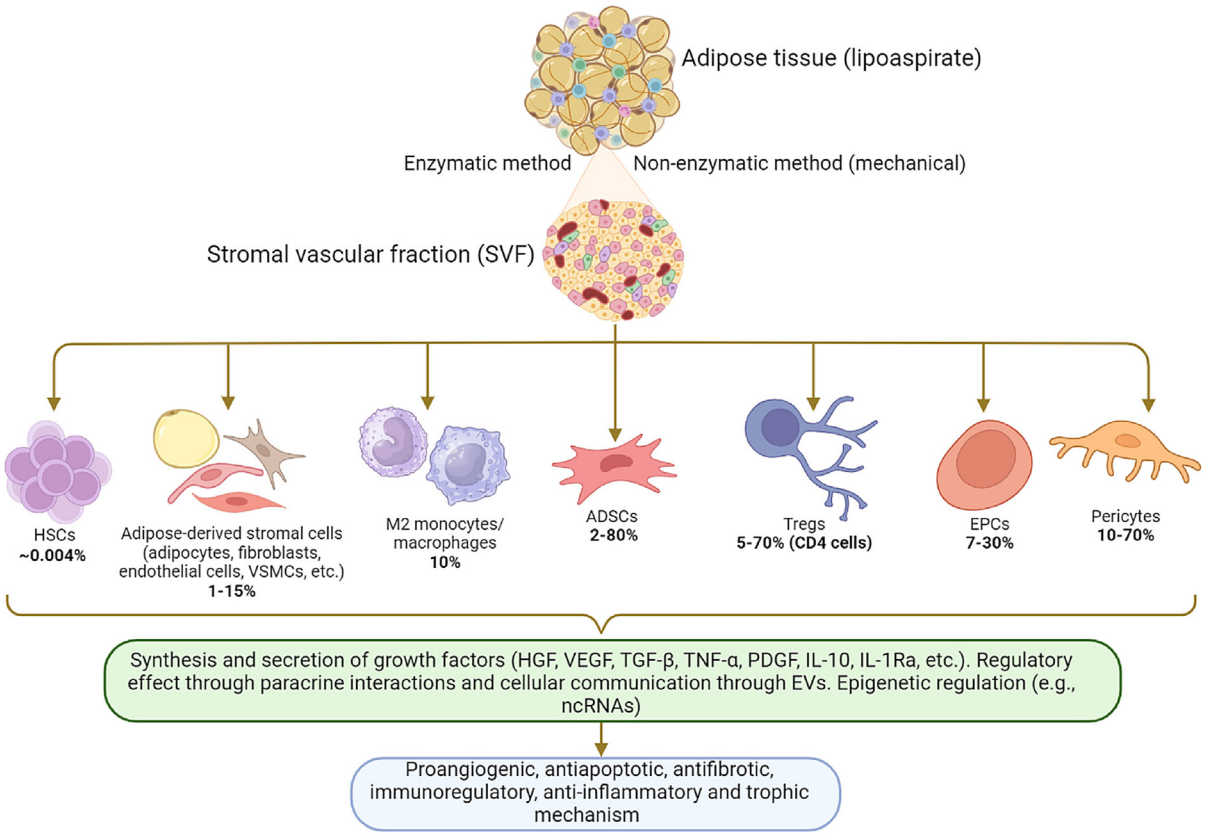

Fig. 1. Cell population of the stromal-vascular fraction (SVF) and their percentage. Adapted from Gareev et al.[14].

of inflammation.[15] TGF-β, on the other hand, is crucial in promoting tissue repair and regeneration by inhibiting the activation and proliferation of immune cells that contribute to inflammatory damage. These anti-inflammatory effects are further enhanced by the ability of SVF cells to reduce the infiltration of pro-inflammatory immune cells into the injured brain tissue. By dampening the inflammatory response, SVF creates a more favorable environment for tissue repair, helping to limit secondary damage and support the brain's natural healing processes. This modulation of inflammation is critical not only for preventing further injury but also for promoting a more controlled and reparative immune response. Another vital mechanism through which SVF exerts its therapeutic effects is the promotion of angiogenesis, which is essential for restoring adequate blood flow and oxygen supply to the areas of the brain affected by hemorrhage.[16] The SVF contains ECs and pericytes, which are key players in the formation of new blood vessels. These cells release angiogenic factors such as vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), both of which are instrumental in initiating and sustaining the process of neovascularization. VEGF stimulates the proliferation and migration of ECs, forming new capillaries, while eNOS plays a crucial role in maintaining vascular tone and ensuring proper blood vessel function. The formation of new blood vessels helps to re-establish blood supply to the ischemic regions of the brain, improving tissue perfusion, and providing the necessary oxygen and nutrients to support neuronal and glial cell survival. Beyond their role in angiogenesis, SVF cells also contribute significantly to neuroprotection through the secretion of neurotrophic factors. These factors, which include brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), are essential for the survival, growth, and maintenance of neurons. BDNF supports the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses, which are critical for functional recovery.[16] NGF, similarly, is involved in the maintenance of cholinergic neurons and plays a role in the repair of neural circuits. By providing these neurotrophic factors, SVF cells help to protect neurons from apoptosis (programmed cell death) and support the repair of damaged neural networks, thereby enhancing the brain's ability to recover function after an injury. Another key aspect of SVF's therapeutic action is its ability to reduce oxidative stress and prevent apoptosis in the brain.[17] Oxidative stress, resulting from an imbalance between the production of reactive oxygen species (ROS) and the brain's antioxidant defenses, is a significant contributor to neuronal death following ICH. SVF cells help to mitigate oxidative stress by enhancing the brain's antioxidant capacity, which in turn reduces the levels of ROS and minimizes oxidative damage to neurons. This reduction in oxidative stress not only protects neurons from damage but also helps to preserve the integrity of the BBB, which is often compromised following an ICH. Immunomodulation is another crucial mechanism by which SVF exerts its protective effects following ICH.[17] The immune-modulating properties of MSCs within the SVF are particularly important in this context. These cells interact with various immune cells, including T cells, macrophages, and dendritic cells, to shift the immune response from a predominantly pro-inflammatory state to a more anti-inflammatory and tissue-reparative state. This shift is critical for reducing immune-mediated damage to brain tissue and promoting an environment conducive to healing and recovery. For instance, MSCs can induce the generation of regulatory T cells, which help to suppress excessive immune responses and prevent further damage to the brain. They also modulate the activity of macrophages, encouraging a transition from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, which is associated with tissue

repair and regeneration.[17] While the direct differentiation of SVF cells into neural or glial cells is not the primary mechanism through which they exert their therapeutic effects, the ability of MSCs and other progenitor cells within the SVF to differentiate into various cell types can still contribute significantly to tissue repair and regeneration. This differentiation potential allows SVF cells to integrate into the host tissue and participate in the reconstruction of damaged neural networks, providing structural support and aiding in the restoration of neurological function. The integration of these cells into the brain's existing cellular architecture may help to rebuild the neural circuits disrupted by hemorrhage, further supporting functional recovery.

2.3. Exosomes

Among the variety of substances secreted by SVF cells into the external environment (intercellular space), extracellular vesicles (EVs) (exosomes or microvesicles) play a special role. Being enclosed in a membrane like the membrane of the cell itself, they can carry both small portions of the usual cytoplasmic content and completely defined sets of biologically active molecules.[18] Exosomes 30–100 nm in size are formed from early endosomes, from which they receive a number of membrane proteins, such as proteins of the main histocompatibility complex, receptors, tetraspanins, etc. Proteins, RNA and DNA, enter exosomes from the cytoplasm of the mother cell, using adenosine triphosphate (ATP)-dependent transport. The main function of exosomes is the ability to transport information from their donor cells to recipient cells (target cells).[19] ECs also secrete exosomes with a specific set of factors (e.g., VEGF and TGF-β), and neighboring ECs can act as target cells for binding to these exosomes, which ultimately promotes growth, migration, and neovascularization.[20] ECs can activate the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway by increasing the expression of chemokine ligand 1 (CXCL-1), inducing epidermal growth factor (EGF) secretion, and promote angiogenesis.[21–22] .

After suffering from oxygen-glucose starvation (secondary damage after ICH), neurons need to restore their metabolism. They can do this with the help of SVF exosomes, which transfer functional mitochondria to neurons as part of exosomes, thereby increasing the survival of neurons and increasing the concentration of neuronal ATP.[23] The secretion of functional mitochondria is an active calcium-dependent process and depends on the activity of a number of enzymes. After receiving mitochondria from the SVF cell population, neurons restore the intracellular concentration of ATP, while if you try to simply supply neurons with ATP, for example, organize delivery by liposomes, the effect will be much weaker.[24] Perhaps, exosomes secreted by SVF cells will be able to protect neurons from the adverse effects of stroke: suppress oxidative stress, supply neurons with intact mitochondria, suppress neuronal death and stimulate plastic changes necessary for post-stroke recovery (Fig. 2).[24,25]

3. Features of using SVF

The mechanism of the therapeutic effect of SVF may depend on the tissue/organ condition. SVF may well act through multiple pathways, and its biological activity may be determined by the host tissue microenvironment. Moreover, the use of SVF may be more effective than the use of a single population of its cells (e.g., isolated ADSCs from SVF), where this effectiveness is achieved due to the synergy between SVF cells. On the other hand, SVF-based therapy is usually performed in a single-step intraoperative manner, and paracrine signaling of different cell types contained in SVF, along with ADSCs, may be more effective than the exclusive administration of ADSCs alone. SVF secretes significantly higher amounts of various soluble signaling factors, such as angiogenic interleukin 8 (IL-8), macrophage inflammatory protein 1α and 1β, as well as reduced levels of the proinflammatory cytokines interferon gamma (IFN-γ) and interleukin 12 (IL-12) compared to single ADSCs.[26,27]

Some studies have shown that SVF isolated from white adipose tissue contained more hematopoietic cells, macrophages, hematopoietic progenitor cells, and immature cells, which together contributed to a higher degree of plasticity than the cell population of SVF isolated from brown adipose tissue.[28,29] Given that excessive visceral fat is detrimental, it is reasonable to ask whether SVF isolated from visceral fat is equally detrimental or dysfunctional compared to SVF from subcutaneous adipose tissue. Some studies have shown that SVF from visceral adipose tissue promotes inflammation, potentially due to a higher proportion of macrophages, natural killer cells, and T cells compared to SVF from subcutaneous fat.[30,31] Furthermore, there is evidence that SVF isolated from the omentum or even serous peritoneal fluid was enriched in T cells and CD45+ leukocytes, respectively.[32] Recent studies show that the regenerative properties of SVF decline with age. Adipose tissue undergoes diverse changes during aging, including redistribution of fat depots, reduction of brown fat, functional decline of ADSCs, accumulation of senescent cells, and immune cell dysregulation. Inflammaging is common in aged adipose tissue. Adipose tissue inflammaging reduces fat plasticity and pathologically promotes adipocyte hypertrophy, fibrosis, and ultimately adipose tissue dysfunction. There is increased infiltration of immune cells into adipose tissue, and these infiltrating immune cells secrete proinflammatory cytokines and chemokines (Fig. 3).[33–35] Taken together, these data suggest that the distribution of adipose precursors varies with age and is dependent on anatomical location. This may impact the functional properties of adipose tissue and, consequently, the regenerative and immunoregulatory behavior of SVF in clinical applications with ICH.

Stem cells are a promising tool for tissue regeneration due to their ability to self-renew and proliferate, as well as their ability to differentiate into a number of different cell lineages. Although there is some controversy surrounding their name and function, it is generally accepted that MSCs have the potential to differentiate into several cell types, including neurons, ECs, vascular smooths muscle cells (VSMCs), and epithelial cells. The advantages associated with the use of MSCs include the ability of MSCs to secrete soluble factors, such as growth factors and anti-inflammatory molecules, which can promote angiogenesis and tissue repair.[36] Hypoxia is a well-known factor in the pathophysiology of ICH. In both in vitro and *in vivo* ICH models, a number of cytokines and chemokines produced by hypoxic tissue are known to attract MSCs to the site of injury.[37–39] Proinflammatory cytokines are required to stimulate the angiogenic, differentiation, proliferative, and immunomodulatory functions of stem cells. Interleukin-1α (IL-1α) and interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α) and interferon are examples of proinflammatory markers that play a role in the pathogenesis of ICH.[37,40] Interestingly, all of these cytokines stimulate the immunomodulatory effects of bone marrow-derived MSCs.[41] IL-6 receptor agonist (IL-6RA) secreted by MSCs inhibits macrophage-activated TNF-α secretion and neutrophil apoptosis, respectively.[42] Thus, this suggests that the use of stem cells has great therapeutic potential in the field of neurosurgery. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have the ability to differentiate into virtually any cell type. However, the clinical application of ESCs has been limited by ethical concerns as well as their potential immunogenicity and carcinogenicity.[36] Nevertheless, the discovery of iPSCs offers the possibility of using the patient's own somatic cells in post-ICH recovery. It is worth exploring alternative ways

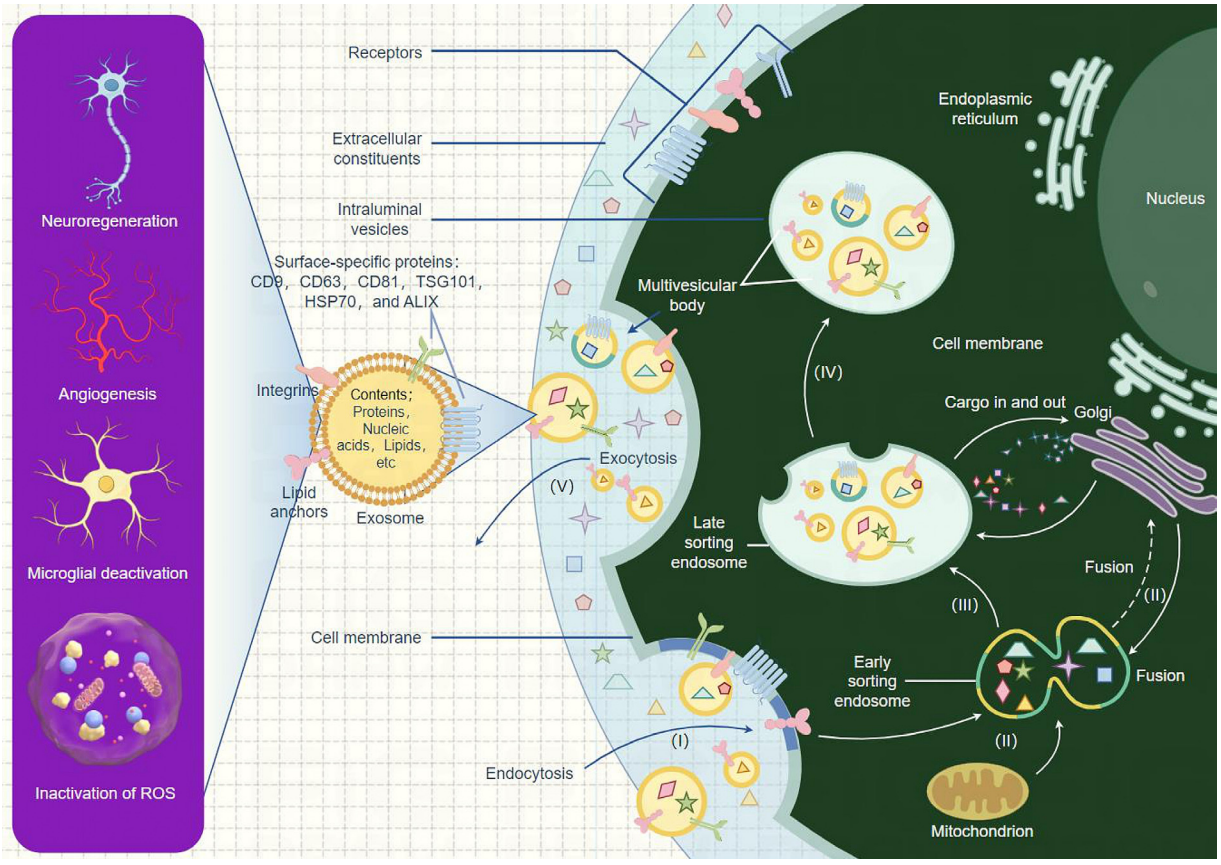

Fig. 2. One of the mechanisms of action after intracerebral hemorrhage (ICH) during transplantation of the stromal-vascular fraction (SVF), in particular through the secretion of exosomes and the effects of their contents, affecting such processes as neuronal recovery, angiogenesis, elimination of the inflammatory process and a decrease in the production of reactive oxygen species (ROS).

of delivering cell therapy that do not require genetic transformation, skilled personnel, or long-term culture. Therefore, SVF may serve as an alternative source of cell therapy in optimizing post-ICH recovery outcomes (Table 1).

4. Route of administration

In addition to the properties of SVF, the effectiveness of therapy is also affected by the method of its transplantation in VNC. Several routes of administration of cell substrates have been developed, each of which has its own characteristics, advantages and complications. It should be noted that the optimal method of transplantation has not yet been established. Therefore, it is important to consider this issue for the future use of SVF. It is known that the most common complication of VNC is secondary brain damage due to compression of the parenchyma by a hematoma with subsequent formation of an ischemic area. Intracerebral stereotactic administration allows delivering cells directly to the ischemic area. With this type of administration, SVF can be delivered in the most targeted manner. However, it should be taken into account that an unfavorable microenvironment is created in the ischemic focus, including for the transplanted cells. The closer the transplanted cells are to this focus, the fewer of them survive after administration. The disadvantages of intracerebral transplantation also include its high invasiveness, additional brain trauma and associated side effects after neurosurgical manipulation.[43–44] Intraventricular and endolumbar administration are less invasive, but infusion into the cerebrospinal fluid spaces may result in cell adhesion to the ependymal lining of the brain ventricles, resulting in occlusive hydrocephalus.[43] A noninvasive method of administration is intranasal transplantation. It has been shown that cells delivered in this way can penetrate the BBB in small quantities and migrate to the damaged area, although the mechanisms of such migration have not been sufficiently studied.[43,45] No side effects have been reported with intranasal administration of MSCs.[46]

The most promising for clinical use is systemic intra-arterial and intravenous administration. Intravenous administration is safer and more widely available, but most of the cells are retained in the parenchymatous organs (lungs, liver, spleen and even kidneys), which can reduce the delivery of SVF to the brain and functional recovery compared to intra-arterial administration. Intra-arterial transplantation of MSCs has demonstrated the best therapeutic efficacy, providing their targeted delivery to the cerebral vessels, bypassing peripheral organs.[47–48] However, a number of authors reported a risk of embolic strokes with this method of MSCs administration.[49–50] This is especially true for the use of SVF, since SVF contains adipocytes. However, embolic complications can be avoided by observing the selection of the optimal amount, rate and conditions of SVF administration. Fig. 4 and Table 2 demonstrate possible routes of SVF administration in the treatment of post-ICH condition with possible advantages and disadvantages.

5. Preclinical evidence supporting SVF therapy for ICH

Animal models have been extensively used to study the pathophysiology of ICH and to evaluate potential therapeutic interven-

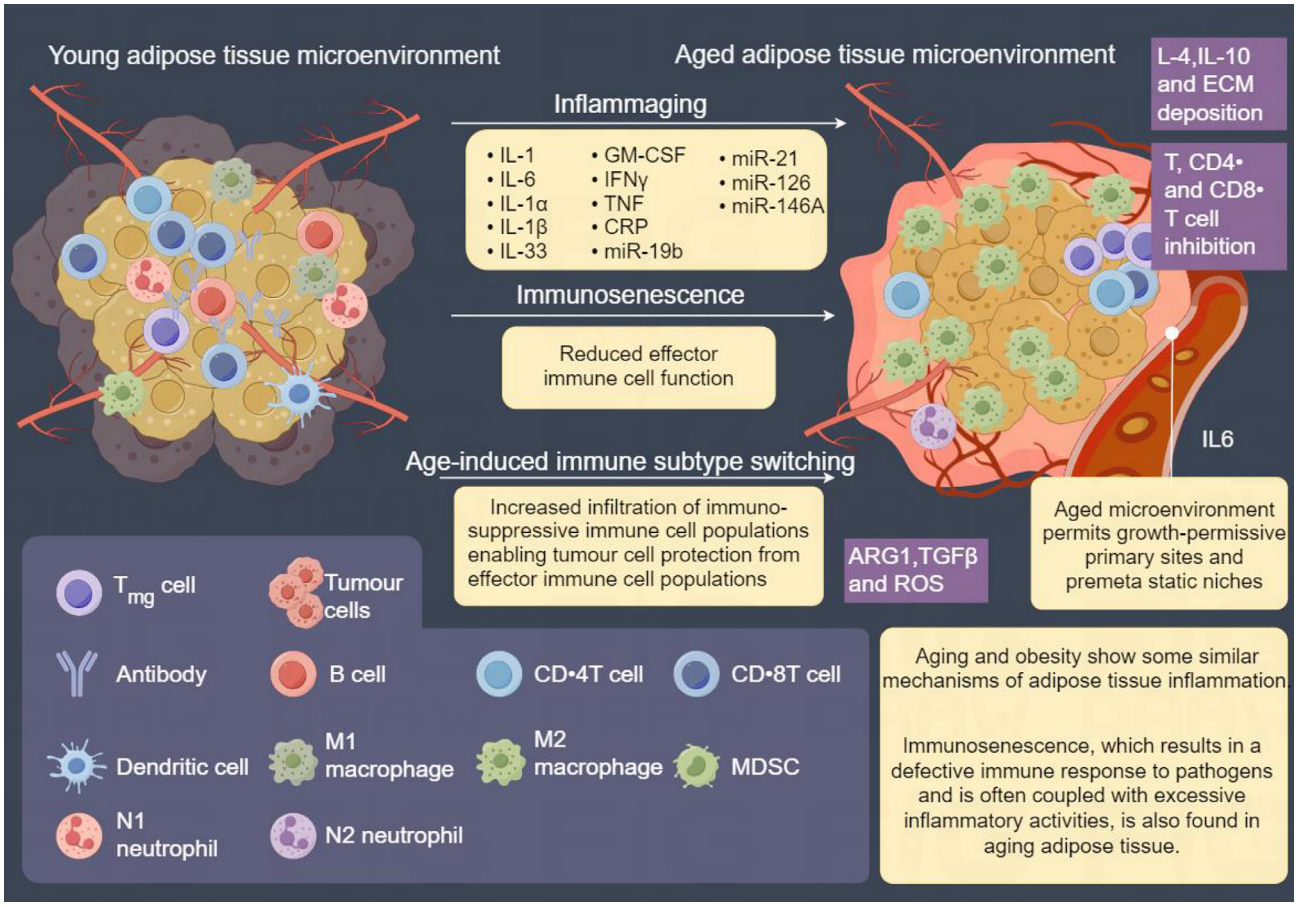

Fig. 3. Adipose tissue microenvironments during aging.

tions. Commonly used models include the collagenase-induced ICH model and the autologous blood injection model. In these models, SVF therapy has been tested for its ability to reduce brain injury, promote tissue repair, and improve neurological outcomes.

Numerous preclinical studies have demonstrated the therapeutic potential of SVF in animal models of ICH. Wan et al. conducted a study in a rat model of collagenase-induced ICH, where they observed that SVF treatment significantly reduced brain edema and levels of pro-inflammatory cytokines, including TNF-α and IL-1β.[51] The study also reported improved neurological function in SVF-treated rats compared to controls. Dykstra et al. investigated the effects of SVF therapy in a mouse model of ICH.[30] They found that SVF treatment led to increased expression of angiogenic factors such as VEGF and eNOS, resulting in enhanced blood vessel formation and improved functional recovery. Zhang et al. evaluated the neuroprotective effects of SVF in a rat model of ICH.[52] Their study demonstrated that SVF treatment reduced oxidative stress markers, including malondialdehyde (MDA) and ROS, while increasing levels of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). These effects were associated with reduced neuronal apoptosis and improved neurological outcomes. Gandolfi et al. explored the immunomodulatory effects of SVF in a rat model of ICH.[53] They reported that SVF treatment reduced the infiltration of pro-inflammatory immune cells, such as neutrophils and macrophages, into the brain, while increasing the presence of anti-inflammatory macrophages and regulatory T cells. This shift in the immune response contributed to a more favorable environment for brain repair. A study by Al-Kharboosh et al. investigated the impact of SVF therapy on functional recovery in a mouse model of ICH.[54] The researchers found that SVF-treated mice exhibited significant improvements in motor coordination and cognitive function compared to untreated controls. These findings suggest that SVF therapy may enhance the recovery of neurological function following ICH.

6. Clinical studies on SVF for ICH

The translation of SVF therapy from preclinical models to clinical application is in its early stages. Several small-scale clinical trials and case studies have been conducted to evaluate the safety, feasibility, and preliminary efficacy of SVF therapy in patients with ICH.

Lee et al. conducted a pilot study to assess the safety and feasibility of SVF therapy in patients with acute ICH.[55] The study involved the intrathecal administration of autologous SVF cells in a small cohort of patients. The results indicated that the treatment was well-tolerated, with no serious adverse events reported. Moreover, some patients showed improvements in neurological function, although the sample size was too small to draw definitive conclusions. Several case reports have documented the use of SVF therapy in patients with ICH. Michalek et al. reported the case of a 65-year-old male patient with a large ICH who received SVF therapy in combination with conventional treatment.[56] The patient showed significant improvement in neurological function and a reduction in hematoma size on follow-up imaging. Another case report by Ferreira et al. described a patient with chronic ICH who experienced functional recovery following SVF therapy.[57] These case reports provide preliminary evidence of the potential benefits of SVF therapy, although larger, controlled studies are needed to confirm these findings.

Table 1
Advantages and disadvantages of stromal vascular fraction (SVF) compared to mesenchymal stromal cells (MSCs), embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) currently used in experimental therapy for intracerebral hemorrhage (ICH).

Cell type	Source	Advantages	Disadvantages
SVF	Adipose tissue	– Obtained and applied on the same day; –No histocompatibility barriers (autologous tissue); –Heterogeneous structure; –Physiologically relevant; –Availability; –High safety index and minimal toxicity	–The field of application in neurosurgery is in its infancy; –Short shelf life; –Requires multiple injections; –The degree of prolonged effectiveness is unknown and little is known about the influence of age, gender, and comorbidities on the effectiveness of SVF
MSCs	Bone marrow	–Promotes neovascularization	–Invasive procedure; –Consequences for the donor with the need to stay in a medical institution after the procedure; –Restrictions in receiving
	Adipose tissue	–Widely characterized; –Availability; –Abundance of cells; –Low donor morbidity and production of a number of growth factors	– Heterogeneous cell population
	Hair follicles	–Non-invasive method; –High proliferative capacity	–Limitations in obtaining; –Poorly studied and additional research is needed regarding the restoration of the ICH
	Amniotic fluid	–High proliferative capacity	–Limitations in obtaining; –Poorly studied and additional research is needed regarding the restoration of the ICH
	Umbilical cord blood	–High proliferative capacity; –Availability	–Poorly studied and additional research is needed regarding the restoration of the ICH
ESCs	Human embryos	–Can be differentiated into any brain cell type and is suitable for in vitro research models	–Ethical issues; –Launch of oncogenesis; –Labor-intensive differentiation process
iPSCs	Reprogrammed cells from adult tissues	–Can be differentiated into any brain cell type and is suitable for in vitro research models; –There are no ethical issues	–Low efficiency of reprogramming and differentiation; –Launch of oncogenesis; –Labor-intensive differentiation process

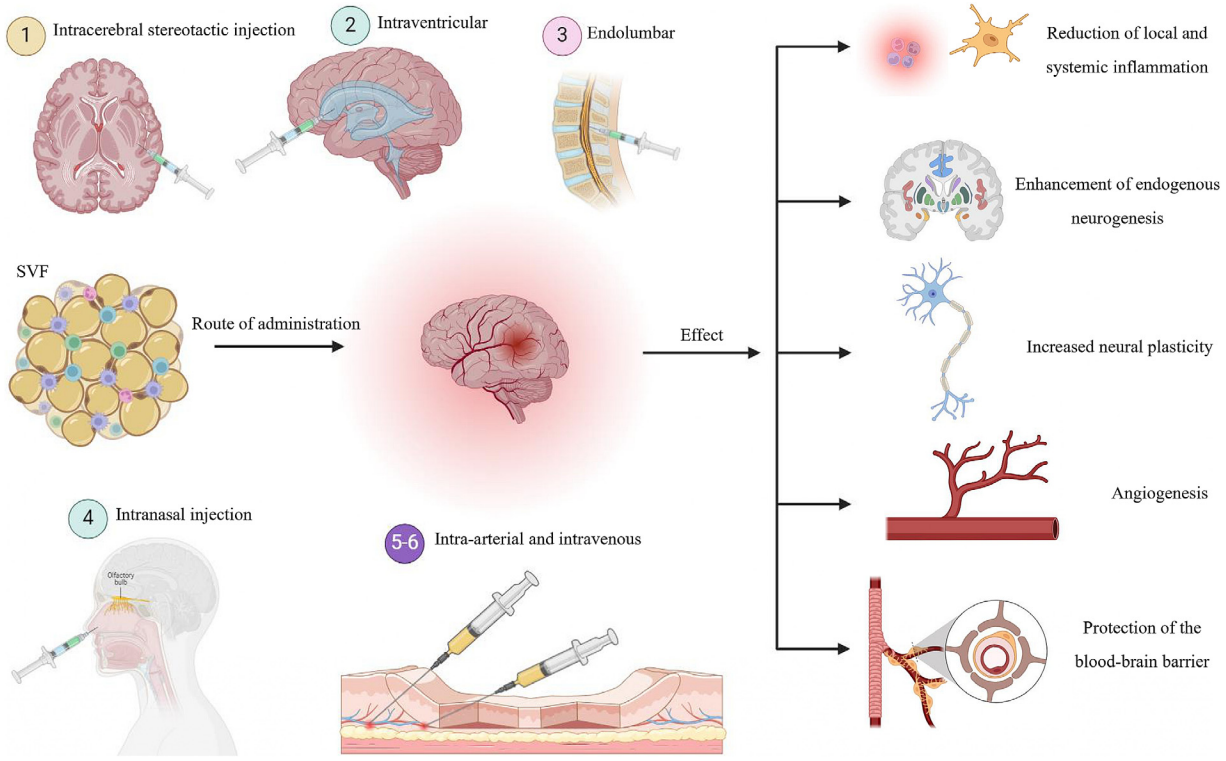

Fig. 4. Possible routes of administration of stromal-vascular fraction (SVF) in the treatment of intracerebral hemorrhage (ICH).

Given the promising preclinical and early clinical evidence, several clinical trials are currently underway to further evaluate the safety, efficacy, and mechanisms of action of SVF therapy in ICH patients. The ongoing phase I/II trial (NCT04063215) aims to investigate the safety and efficacy of autologous SVF therapy in patients with acute ICH.[58] The study plans to enroll 50 participants and will

Table 2
Advantages and disadvantages of possible routes of administration of stromal vascular fraction (SVF) in the treatment of intracerebral hemorrhage (ICH).

Routes of administration	Advantages	Disadvantages
Intracerebral stereotactic injection	– Delivery of SVF to the maximum possible address	–Unfavorable microenvironment for the survival of transplanted SVF; –High invasiveness; –Limitations in the use of this method in the acute period of ICH
Intraventricular injection	–Minimally invasive method	–Adhesion of SVF with the development of occlusive hydrocephalus is possible
Endolumbar injection	–Minimally invasive method	–Adhesion of SVF with the development of occlusive hydrocephalus is possible
Intranasal injection	–Non-invasive; –Overcoming the BBB and direct nose-to-brain deliver; –Rapid onset of action; –High patient compliance; –Self-administration by patients	–Irreversible damage of nasal mucosa; –SVF dose loss due to improper use; –The state of the nasal cavity; –Unclear mechanism
Intra-arterial injection	–Minimally invasive method; – It also has a systemic effect on the periphery	– Emboli formation is possible
Intravenous injection	–Minimally invasive method; – It also has a systemic effect on the periphery	–Bioavailability

assess neurological outcomes, imaging biomarkers, and safety parameters over a 12-month follow-up period. The results of this trial are anticipated to provide valuable insights into the potential of SVF therapy for ICH. The long-term safety and efficacy of SVF therapy are being evaluated in an ongoing follow-up study (NCT05232903).[59] This study aims to monitor patients who have received SVF therapy for up to five years, assessing long-term outcomes such as functional recovery, quality of life, and potential adverse events. The findings from this study will be crucial for determining the durability of the therapeutic effects of SVF.

7. Challenges in SVF therapy for ICH

While SVF therapy shows promise as a treatment for ICH, several challenges must be addressed to ensure its successful translation into clinical practice. The heterogeneity of SVF, which contributes to its therapeutic potential, also presents a challenge in terms of standardization and reproducibility.[60] The composition of SVF can vary depending on the method of isolation, the characteristics of the donor (e.g., age, health status), and the processing techniques used. This variability can impact the consistency and efficacy of the treatment.[61] Efforts are needed to develop standardized protocols for SVF isolation, characterization, and quality control. The optimal delivery method for SVF therapy in ICH remains to be determined. While intrathecal injection has been used in some studies, other delivery routes, such as intravenous or intra-arterial administration, may also be feasible.[62] The choice of delivery method could influence the distribution of SVF cells within the brain and their ability to reach the site of injury. Preclinical studies are needed to compare the biodistribution and therapeutic efficacy of different delivery methods.[63] The timing of SVF administration is a critical factor that could affect the outcomes of the therapy. Administering SVF too early after ICH may interfere with the acute inflammatory response that is necessary for clearing the hematoma, while delayed administration may miss the window of opportunity for effective tissue repair.[28,64] Further research is needed to determine the optimal timing of SVF therapy in relation to the onset of ICH. The long-term safety and efficacy of SVF therapy in ICH have yet to be fully established.[32] While early studies have shown promising results, longer follow-up periods and larger patient cohorts are needed to determine whether SVF therapy can provide sustained benefits and reduce the risk of complications.[65,66] Long-term monitoring of patients who have received SVF therapy is essential for identifying any delayed adverse effects and for assessing the durability of the therapeutic effects. As SVF therapy progresses towards clinical application, regulatory and ethical considerations must be addressed.[67] Ensuring patient safety, obtaining informed consent, and adhering to regulatory guidelines for cell-based therapies are essential for the successful translation of SVF therapy into clinical practice. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), have established guidelines for the use of cell-based therapies, which must be followed to ensure the safety and efficacy of SVF treatment.

8. Future directions and limitations

Developing standardized protocols for the isolation and processing of SVF is crucial for ensuring consistency and reproducibility across studies. This could involve the establishment of guidelines for donor selection, tissue processing, and cell characterization. Efforts should also be made to develop quality control measures to ensure the potency and purity of SVF products. Moreover, further research is needed to optimize the delivery methods for SVF therapy in ICH. Preclinical studies could explore the biodistribution of SVF cells following different delivery routes, and clinical trials could compare the efficacy of various administration methods. Innovative delivery techniques, such as targeted delivery systems or the use of biomaterials to enhance cell retention at the injury site, could also be explored.

Understanding the precise mechanisms through which SVF exerts its therapeutic effects is essential for refining the treatment and identifying potential biomarkers of response. Advanced imaging techniques, such as functional MRI and PET, could be used to monitor the effects of SVF therapy on brain function and inflammation. Molecular studies could also investigate the signaling pathways and gene expression profiles associated with SVF-mediated neuroprotection and tissue repair. Exploring the potential of combination therapies, where SVF is used alongside other treatments such as hyperbaric oxygen therapy (HBOT), neuroprotective agents, or rehabilitation, could enhance the overall therapeutic outcomes. Clinical trials investigating such combinations could provide valuable insights into synergistic effects and help identify the most effective treatment regimens for ICH. Combination therapies may also address multiple aspects of ICH pathology, such as reducing inflammation, promoting angiogenesis, and enhancing neuroplasticity.

Given the variability in patient responses to cell-based therapies, personalized medicine approaches could be explored to tailor SVF therapy to individual patients. This could involve the use of

biomarkers to identify patients who are most likely to benefit from SVF therapy or the development of patient-specific SVF products. Personalized approaches could enhance the efficacy and safety of SVF therapy and improve patient outcomes.

To establish the efficacy and safety of SVF therapy for ICH, large-scale, randomized controlled trials are needed. These trials should include diverse patient populations and long-term follow-up to assess the durability of the therapeutic effects. The results of such trials will be critical for the regulatory approval of SVF therapy and its integration into clinical practice.

As SVF therapy moves towards clinical application, considerations of cost-effectiveness and accessibility will become increasingly important. The development of cost-effective and scalable methods for SVF production and delivery will be essential for making the therapy accessible to a broad range of patients. Economic evaluations should also be conducted to assess the cost-effectiveness of SVF therapy compared to standard care.

9. Conclusions

SVF therapy presents a revolutionary approach to addressing the multifaceted challenges posed by ICH, a condition that remains one of the deadliest and most debilitating forms of stroke. Traditional therapeutic approaches, which focus primarily on stabilizing the patient and preventing further complications, often fail to address the extensive neurological damage and long-term disabilities resulting from ICH. SVF therapy, with its regenerative capabilities, represents a paradigm shift by targeting the underlying pathophysiological processes of ICH through cellular mechanisms that facilitate repair, regeneration, and recovery. The diverse cellular composition of SVF, comprising MSCs, endothelial cells, pericytes, immune cells, and progenitor cells, enables it to address several critical aspects of ICH pathology simultaneously. MSCs, through the secretion of anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), effectively modulate inflammation, reducing secondary brain injury caused by the excessive inflammatory response. The endothelial and pericyte populations within SVF play a pivotal role in promoting angiogenesis and vascular repair, which are essential for restoring blood flow and oxygenation to ischemic brain tissues. Furthermore, neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), secreted by SVF cells, protect neurons from apoptosis, promote synaptic repair, and encourage the formation of new neural connections. These synergistic actions make SVF uniquely suited to addressing the complex pathophysiology of ICH. Preclinical studies have provided compelling evidence for the efficacy of SVF therapy, demonstrating significant improvements in animal models of ICH. These include reductions in brain edema, oxidative stress, and inflammation; enhanced angiogenesis and neuroprotection; and meaningful functional recovery. Notably, these studies have shown that SVF therapy not only mitigates the immediate consequences of ICH but also promotes long-term recovery, making it a comprehensive therapeutic strategy. Early-phase clinical trials and case studies in humans, while limited in scope, have yielded encouraging results. These studies have demonstrated that SVF therapy is feasible, safe, and capable of improving neurological outcomes in patients with acute and chronic ICH. Patients receiving SVF therapy have shown reductions in hematoma size, improved motor and cognitive functions, and enhanced quality of life. While these findings highlight the potential of SVF therapy, larger, well-controlled clinical trials are necessary to validate these results and establish its efficacy in broader patient populations. Despite its promise, several challenges must be overcome to facilitate the clinical translation of SVF therapy. A key challenge lies in the inherent heterogeneity of the SVF cell population. While this heterogeneity contributes to its therapeutic versatility, it also leads to variability in treatment outcomes, underscoring the need for standardized protocols for SVF isolation, characterization, and administration. Developing quality control measures to ensure the consistency, potency, and safety of SVF products is critical for its successful clinical implementation. The choice of delivery method is another critical factor influencing the efficacy of SVF therapy. While intrathecal, intravenous, and intra-arterial delivery routes have all been explored, further research is needed to determine the optimal method for targeting SVF cells to the site of brain injury while minimizing potential risks. The timing of SVF administration is equally important, as early intervention could interfere with necessary inflammatory processes, whereas delayed therapy may miss the window of opportunity for effective tissue repair. Long-term safety and efficacy remain areas requiring further investigation. Although short-term studies have demonstrated that SVF therapy is well-tolerated, extended follow-up is essential to identify potential delayed adverse effects and assess the durability of therapeutic benefits. Addressing these gaps through rigorous, long-term studies will be pivotal for building confidence in SVF therapy as a viable treatment option. The future of SVF therapy lies in its integration with other therapeutic modalities to maximize its benefits. Combination therapies, where SVF is used alongside neuroprotective agents, hyperbaric oxygen therapy, or advanced rehabilitation techniques, hold promise for enhancing its therapeutic effects. Personalized medicine approaches, leveraging biomarkers to tailor SVF therapy to individual patient profiles, could further optimize treatment outcomes and minimize risks. Advancements in bioengineering and technology may also enhance the efficacy of SVF therapy. For instance, innovations such as biomaterial scaffolds or targeted delivery systems could improve cell retention and localization at the injury site, boosting therapeutic efficacy. Furthermore, mechanistic studies employing advanced imaging techniques and molecular analyses could provide deeper insights into the pathways through which SVF exerts its effects, paving the way for more targeted and efficient therapies. Large-scale, randomized controlled trials are essential for validating the efficacy and safety of SVF therapy. These trials should encompass diverse patient populations, assess long-term outcomes, and address economic considerations to ensure the therapy's accessibility and affordability. The development of cost-effective and scalable methods for SVF production and delivery will be crucial for its integration into routine clinical practice. The implications of SVF therapy extend beyond ICH, as its regenerative properties hold potential for addressing a wide range of neurological disorders and injuries. By advancing our understanding of SVF and refining its application, researchers can unlock new possibilities in regenerative medicine, offering hope to patients with conditions previously considered untreatable.

In conclusion, SVF therapy represents a groundbreaking advance in the treatment of intracerebral hemorrhage, offering a comprehensive approach that transcends the limitations of conventional therapies. By harnessing the regenerative potential of adipose-derived cells, SVF therapy addresses the root causes of brain injury and promotes true recovery, rather than mere symptom management. While challenges remain, ongoing research, innovation, and clinical trials hold the promise of overcoming these obstacles and realizing the full potential of SVF therapy. With its ability to improve outcomes and quality of life for patients, SVF therapy has the potential to redefine the therapeutic landscape for ICH, offering hope to millions affected by this devastating condition. Through continued dedication to research and development, SVF therapy may become a cornerstone of ICH management and a beacon of progress in regenerative medicine.

ARRIVE guidelines statement

The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

CRediT authorship contribution statement

Ilgiz Gareev: Writing – review & editing, Writing – original draft, Conceptualization. **Ozal Beylerli:** Visualization, Validation, Methodology, Investigation. **Albert Sufianov:** Resources, Investigation. **Valentin Pavlov:** Formal analysis, Data curation. **Huaizhang Shi:** Supervision, Project administration, Formal analysis.

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Data availability

All relevant raw data are freely available to any researchers who wish to use them for non-commercial purposes while preserving any necessary confidentiality and anonymity. The datasets are available on request to the corresponding author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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