Chapter 9
Modification of Bone Marrow Stem Cells for Homing and Survival During Cerebral Ischemia

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Abstract Over the last decade, major advances have been made in stem cell-based therapy for ischemic stroke, which is one of the leading causes of death and disability worldwide. Various stem cells from bone marrow, such as mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and endothelial progenitor cells (EPCs), have shown therapeutic potential for stroke. Concomitant with these exciting findings are some fundamental bottlenecks that must be overcome in order to accelerate their clinical translation, including the low survival and engraftment caused by the harsh microenvironment after transplantation. In this chapter, strategies such as gene modification, hypoxia/growth factor preconditioning, and biomaterial-based methods to improve cell survival and homing are summarized, and the potential strategies for their future application are also discussed.

Keywords Bone marrow stem cells • Modification • Homing • Survival • Ischemia

9.1 Introduction

Stroke is the third leading cause of mortality and the leading cause of long-term disability in the United States. Approximately 8,000,000 people suffer a stroke, and more than 140,000 people die each year. Ischemic stroke accounts for over 80 % of total stroke patients [126]. Though extensive neuroprotection and regenerative studies have been performed, only tissue plasminogen activator (tPA) has been proven to be effective. However, due to its narrow therapeutic time window (less than 4.5 h) and hemorrhagic complication, fewer than 5 % of stroke patients are able to benefit from tPA, and even among those, only 10 % return to independent living [82].

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Recently, growing evidence suggests that stem cells, including MSCs, neural stem cells (NSCs), EPCs, and induced pluripotent stem cells (iPS), are beneficial for cerebral ischemia [77, 112]. Among these, bone marrow-derived stem cells (BMSCs) have the most promising therapeutic potential, because a large quantity can be harvested autologously without ethical or immunological issues [120]. However, a number of problems remain unresolved and need specific attention prior to general clinical translation. For example, it is still challenging that stem cell survival, homing, and engraftment rates are low after transplantation in the pathological environment subjected to multiple insults, including ischemia/hypoxia, inflammatory response, and so on, which hamper the benefits and applications of cell-based therapy.

This chapter first summarized recent progress in basic and translational research in the field of BMSC transplantation for ischemic stroke. It then critically discussed how to enhance BMSC-based therapy by improving grafted cell survival and homing to further establish BMSC transplantation therapy as a scientifically proven method in clinical applications.

9.1.1 Basic Concept of Bone Marrow Stem Cells (BMSCs) in Stroke

Bone marrow (BM) consists of heterogeneous stem cell populations, including MSCs, HSCs, EPCs, and very small embryonic-like cells (VSELs). Their neuronal differentiation potential as well as neurotrophic factor secretion capacity has prompted interest in using BM as stem cell donor source for cell-based therapy in stroke.

9.1.1.1 Bone Marrow-Derived Mesenchymal Stem Cells (MSCs)in Stroke

BM-derived MSCs are a population of plastic-adherent fibroblastic cells, with CD29, CD105, and CD73 positive, but lack of hematopoietic surface markers such as CD34 and CD45. MSCs have the potential to differentiate into mesodermal cell lineages to involve in adipogenesis, chrondrogenesis, and osteogenesis [13]. MSCs derived from various donors, including rat, mouse, rabbit, or humans, have been transplanted by intravenous (IV), intra-artery (IA), intracerebral (IC), or intracisternal routes into animals, from different time points (hours to months) after induction of stroke, and have shown to improve functional recovery during cerebral ischemia [112]. Following IV and IC injection, MSCs migrate to the ischemic boundary; however, few cells have been shown to survive, and long-term cell engraftment has not been detected with IV administration [96]. Another study stated that only 3 % of administered cells expressed neuronal markers in vivo [15], which argued with the concept that tissue replacement is likely to be a potential mechanism for this

strategy. More studies support that trophic factors secreted by the MSCs in response to the local microenvironment stimulate endogenous neurogenesis, angiogenesis, and immunomodulation and further improve functional recovery. Higher levels of BDNF, NT3, and VEGF have been detected in the penumbra region 14 days after human MSC transplantation [5]. Increased VEGF and bFGF drive angiogenesis and facilitate regional blood flow [53]. In addition to secreting trophic factors, MSCs were also detected to influence astrocyte survival and astrocyte-related trophic factor expression after ischemic insult, by activating kinase pathways and protein functions [67]. Up to date, clinical reports also reveal that MSCs significantly improve patients' functional recovery without adverse side effects, probably through neuronal differentiation or secreting anti-inflammatory as well as neurotrophic factors [11].

9.1.1.2 HSC

Quiescent of CD34+ HSCs are able to migrate quickly from bone marrow to blood circulation in response to cerebral ischemia, which is induced by a wide array of chemokines and cytokines, including stromal cell-derived factor-1 (SDF-1) and granulocyte-colony-stimulating factor (G-CSF) [50]. During stroke, HSCs exit from bone marrow, migrate to the brain, adhere to the vascular wall, and cross over the blood–brain barrier (BBB), mediated by SDF-1/CXCR4 axis or G-CSF. This recruitment of HSCs from BM to stroke-induced lesion area has been employed in clinical protocols, for the creation of ample supply of HSCs for brain repair [10]. Both experimental and clinical studies have demonstrated the safety and feasibility of HSCs-based therapy for ischemic stroke. Intracerebral implantation of CD34+ HSCs promoted angiogenesis and neurogenesis and increased the local cortical blood flow in the ischemic hemisphere in ischemic rats [100] and mice [107]. A small clinical study demonstrated that by autologously IA injection of CD34+ cells into five stroke patients, all patients showed behavior recovery and infarct reduction, suggesting the potential of direct IA infusion of autologous CD34+ selected cells for the treatment of stroke [4].

9.1.1.3 EPC

In 1997, Asahara and coworkers first isolated Flk-1+/CD34+ cells from human peripheral blood, which were defined as EPCs. In that study they found that these cells could integrate into blood vessels when transplanted into a hind-limb ischemic mouse model [1]. EPCs were usually generated and maintained in bone marrow and could migrate into lesion region to help blood vessel remodeling and repair [71]. Recent studies showed that EPC transplantation could promote cerebral blood flow, reduce infarct volume and neuronal cell death, increase focal angiogenesis and neurogenesis, and improve neurobehavioral recovery after ischemia [26]. Grafted EPCs could either secrete neurotrophic factors, which is supported by the evidence that

EPC medium could also promote angiogenesis [144], or differentiate into endothelial cells to replace/repair injured ECs and integrate into endogenous blood vessels, which is detected by histological studies [26]. These results support that EPCs have great therapeutic potential for stroke, most possibly through both directly integrating into blood vessels and secreting trophic factors.

9.1.1.4 Very Small Embryonic-Like Cells

In 2006, Ratajczak's group first discovered a nonhematopoietic population that expresses neural lineage markers (GFAP, Nestin, Olig1, Olig2, Sox2, and Musashi-1) and resides in the nonhematopoietic CXCR4+/Sca-1+/lin-/CD45- BM mononuclear cell fraction, named as very small embryonic-like cells (VSELs) [90]. The number of circulating VSELs in PB increases in mice after experimental stroke [55] and in stroke patients [89], suggesting that VSELs residing in adult tissues or mobilized into PB are a potent source of adult tissue-derived stem cells that can be used for regenerative medicine, particularly for neural repair after stroke. Ratajczak et al. observed increased gene expression of both pluripotent and NSC markers in PB-borne nucleated cells in stroke patients, resembling what they previously noted in murine stroke model. Further analyses using computer tomography imaging revealed differences in VSEL mobilization between patients with posterior circulation infarcts and patients with partial anterior circulation infarcts [55]. In addition, the observation that murine VSELs are capable of differentiating into neurons, oligodendrocytes, and microglia further encourages us to use these cells as donor grafts for regeneration of a damaged CNS. However, a limitation for clinical application is the small number of VSELs that could be harvested, requiring ex vivo expansion strategy, especially to generate enough supply of VSELs for stroke therapy in clinical setting.

9.1.2 Mechanism of Death of Transplanted Stem Cells During Cerebral Ischemia

Although stem cell transplantation appears to be very promising for stroke, a number of problems remain unresolved and need specific attention in order to improve therapeutic efficacy for further successful clinical translation, including low survival and engraftment of transplanted cells in the brain subjected to multiple insults including ischemia, reactive oxygen species (ROS) generation, inflammatory response, apoptotic cascade activation, and so on.

Accumulating evidence demonstrates that less than 10% of transplanted stem cells could survive in the lesion site after transplantation as they are exposed in hostile environment, and cell death is initiated via multiple mechanisms [48]. It's reported that more cells survive when they are transplanted into sham animals (no brain injury) compared to injured animals [3], indicating that factors in the lesion

site induce death of the transplanted cells. These factors include but not limited to time after injury [47], distance from the transplantation site to the lesion site [86], state of the cells transplanted (differentiated or undifferentiated) [59], aging of the cells transplanted [108], host immune response [35], and phagocytic response of host [2]. Subsequent evidence shows that delivery time is the major determinant of the survival of transplanted stem cells. It is reported that NPC survival was significantly reduced following delayed cell delivery [20], which was mediated by the inflammatory milieu.

Cell death is initiated even prior to transplantation, explained by two main mechanisms: detachment of cells from adherent surface and the removal of growth factor, during the procedure of trypsinization and suspension. Inhibition of cell adhesion-induced cell death was first reported in 1994 by Frisch and Francis. They found that when epithelial cells were seeded in medium with the addition of soluble peptide-GRGDSP, which prevented cell attachment by blocking integrins, it resulted in increased apoptosis [28]. This kind of cell death is termed anoikis, which can be rescued by culturing cells on ECM-coated surfaces to promote cell adhesion. For example, oligodendrocyte progenitor cells cultured on glass coverslips coated with fibronectin or laminin showed greater viability compared to those cultured on non-coated surfaces [37]. In vitro study demonstrated that addition of laminin to neural progenitor cells increased the number of neurospheres and reduced cell death in comparison to control groups, while blocking the beta 1 integrin inhibited the effect of laminin, suggesting this is beta 1 integrin mediated [32]. One proposed explanation for detachment-induced cell death is that Bmf released from actin in terms of cytoskeleton stabilization is reduced after cell detachment. Bmf binds to Bcl-2 in mitochondria and neutralizes its antiapoptotic effect, which activates caspase-8, further releasing Bcl-2 from the mitochondria to induce cell death [29].

In addition to detachment-mediated cell death, removal of growth factors also induces apoptosis. Typically, c-Jun amino-terminal kinase (JNK) signaling pathway is activated when trophic support is removed, mediates c-Jun phosphorylation, thus induces the expression of proapoptotic factor-Bcl-2 family (DP5/Hrk). It further demonstrates that DP5 activates a proapoptotic member of the Bcl-2 family-Bax, causes mitochondrial damage, and releases cytochrome c, leading to the formation of apoptotic protease-activating factor 1 (Apaf-1)/caspase-9 complex, which activates caspase-3 resulting in cell apoptosis [138].

Therefore, cell–ECM interactions are reduced, and apoptosis is initiated even prior to transplantation when stem cells are trypsinized as single cells, cell survival is further reduced by needle insertion, and growth factors withdraw during the injection process, as well as hostile environment they confront in the lesion site after transplantation, given the generation of reactive oxygen species (ROS) and inflammatory response mediators in brain postischemia. It is highly accepted that cerebral ischemia caused excessive ROS would induce the apoptosis of the transplanted cells [12]. Our study showed that more than 80 % of grafted cells died within 72 h after administration [110], and our in vitro studies also suggested that exposure of stem cells to culture conditions which mimic the hostile environment in vivo (such as oxygen–glucose deprivation and H2O2 stimulation) led to the apoptosis mediated by ROS [110].

9.1.3 Strategies to Improve BMSC Survival

Both basic studies and clinical evidence strongly support that BMSCs could serve as a promising restorative therapy for stroke. However, as stated above, high stem cell death rate is the main hurdle that hinders the therapy. Scientists in the field propose several strategies to conquer this challenge, including gene modification, preconditioning, and biomaterial-based methods.

9.1.3.1 Gene Modification

After cerebral ischemia, both intrinsic and extrinsic apoptosis pathways are activated [3]. More than 80% of stem cells died after their transplantation, which is mainly caused by the activation of proapoptotic signals. Thus, downregulation of proapoptotic or upregulation of antiapoptotic cues by manipulating gene expression of stem cells posttransplantation may ameliorate the microenvironment and further enhance their survival. Indeed, overexpressing of Bcl-2 in embryonic stem cells (ESCs) increased their survival after injection into ischemic rat brain, as well as enhanced their neuronal differentiation, and improved functional outcome [123].

In addition to regulate apoptotic-related genes, amounting evidence shows that modification of trophic genes in stem cells also has significant impacts on their survival and therapeutic efficacy (Table 9.1). MSCs overexpressing BDNF or GDNF after injection into ischemic rats showed more cell survival, promoted functional recovery, and reduced ischemic damage at 7 and 14 days following MCAO, while rats that received CNTF- or NT3-transfected MSCs showed neither functional recovery nor ischemic damage reduction [57]. Liu et al. found that intravenously administered hMSCs overexpressing PIGF could accumulate in the ischemic lesions, further reduced lesion volume, enhanced angiogenesis, and elicited functional improvement [74]. FGF-2-modified MSCs with HSV-1 greatly reduced infarct volume and improved functional recovery at 14 days after stroke [40]. When surviving, a new apoptosis-inhibiting protein was overexpressed in MSCs and promoted MSCs' survival by 1.3-fold at 4 days and 3.4-fold higher at 14 days posttransplantation, which results in reduced infarct volume and improved neurological function [76].

Besides BMSCs, lots of studies from Dr. Kim's group showed that transplantation of human NSCs overexpressing BDNF [61], VEGF [60], or Akt-1 [61] could produce a two- to threefold increase in cell survival at 2 weeks and 8 weeks posttransplantation, as well as reduce infarct volume and improve functional recovery [171]. Transduction of NPCs with TAT-Hsp70 led to increased number of grafted NPCs, reduced BBB disruption, enhanced postischemic neurogenesis, and increased neurotrophic factor secretion [23].

During the last decade, microRNAs (miRs), a group of short RNA molecules that involve in posttranscriptional downregulation, have gained extensive attention in modulating cell survival. It is reported that miR-210 and miR-107 exert significant

Table 9.1 Enhancement of stem cell survival by gene modification

Ovexpressing genes	Stem cells	Transfecting agents	Stem cell fate	Therapeutic outcome
Bcl-2 [200]	Embryonic stem cells	Electroporation with Bcl-2 plasmid	Increased ES survival after injection	Into ischemic rat brain, as well as enhanced their neuronal differentiation and improved functional outcome
BDNF or GDNF [166]	MSCs	Adenovirus	More cells survival at 7 and 14 days following MCAO	Improved functional recovery and reduced ischemic damage at 7 and 14 days following MCAO
PIGF [175]	hMSCs	Adenovirus	More cells accumulate in the lesion area	Accumulate in the ischemic lesions, further reduce lesion volume, enhance angiogenesis, and elicit functional improvement
FGF-2 [160]	MSCs	HSV-1 vector	N/A	Reduced infarct volume and improved functional recovery
Ang-1 [184]	hMSC	Adenovirus	N/A	Rats receiving Ang-hMSCs exhibited comparable lesion reduction, improved functional recovery, and increased angiogenesis
Survivin [176]	MSCs	Lentiviral vector	Promote MSCs' survival by 1.3-fold at 4 days and 3.4-fold higher at 14 days posttransplantation	Reduced infarct volume and improved neurological function

(continued)

Table 9.1 (continued)

Ovexpressing genes	Stem cells	Transfecting agents	Stem cell fate	Therapeutic outcome
BDNF [61]	NSCs	Adenovirus	Threefold increase in cell survival at 2 weeks and 8 weeks post injection	Renewed angiogenesis, induce behavioral improvement in ICH animals
Akt-1 [61]	NSCs	Retroviral vector	50–100 % increased cell survival at 2 and 8 weeks posttransplantation	Induced behavioral improvement
Bcl-XL [170]	hNSCs	Retroviral vector	Number of hNSCs were 1.5-fold higher at 2 weeks and 10-fold higher at 7 weeks than controls posttransplantation	Improved locomotor scores and enhanced accuracy of hind-limb placement in a grid walk
HSP-70 [154]	NPCs; MSCs	TAT-Hsp70 protein transduction	Increased intracerebral numbers of grafted NPCs	Reduced BBB disruption, enhanced postischemic neurogenesis, and increased neurotrophic factor secretion; decreased apoptosis in the infarcted tissue and improved cardiac function
HSP 27 [180]		Lentiviral vector	Increased MSCs' survival in vitro and in vivo	
HGF [209]	MSC	HSV-1	N/A	Decreased apoptosis of neurons and reduced neurologic deficits and infarcts
CXCR4 [207]	MSC	Lentivirus	A significant increase in the number of eGFP-positive MSCs in the infarct areas	A reduction in the volume of the cerebral infarction and improved neurological function

(continued)

Table 9.1 (continued)

Ovexpressing genes	Stem cells	Transfecting agents	Stem cell fate	Therapeutic outcome
VEGF [169, 210]	NSC	Retroviral vector	2–3 fold increase in cell survival at 2 weeks and 8 weeks posttransplantation	Increased angiogenesis and behavioral recovery in mouse ICH model; improved focal angiogenesis and the Neurological Severity Scale score
	MSC	Plasmid transfection with lipofactamine	Improved cell viability	Enhanced the capillary formation in the infarction region and eventually attenuated left ventricular remodeling
		Facially amphipathic bile acid-modified polyethyleneimine (BA-PEI) conjugates [182]		

antiapoptotic effects in BMSCs by targeting caspase-8-associated protein-2 and programmed cell death-10 [81]. Pharmacological agents, including diazoxide [84], can induce protective miRs expression. Besides miRs, a recent investigation elucidated that preconditioning of MSCs with specific cell-free DNAs (cfDNAs) increased cell survival via Toll-like receptor 9 (TLR9) and translocation of nuclear factor-kappa B (NFkB) [54]. This evidence highlights the possibility that miRs and cfDNAs may be potential new targets to promote stem cell survival after transplantation.

Collectively, these exciting results suggest that gene modification is a promising strategy to increase cell survival after transplantation, and these enhanced cell survivals could contribute to reduced infarcts and improved behavioral recovery through neuronal differentiation and promoted trophic factor secretion.

9.1.3.2 Precondition-Based Method

Gene modification takes the risk that uncontrolled expression of introducing gene may have adverse effects and induce tumor formation on normal brain. Recent studies show that precondition strategy including hypoxia preconditioning, growth factor preconditioning, and antiapoptosis drug preconditioning could be a safe and efficient method [136]. Up to now, a number of sublethal insults including hypoxia [131], anoxia [119], hydrogen sulfide (H2S) [127], hydrogen peroxide (H2O2) [141], as well as growth factors, such as erythropoietin (EPO) [68], stromal-derived

factor-1 (SDF-1) [139], insulin-like growth factor-1 (IGF-1) [78], heat shock proteins (HSPs) [117], or pharmacological agents such as melatonin [110], minocycline [94], isoflurane [52], and lipopolysaccharide (LPS) [132], have been tested in stem cells (Table 9.2).

Sublethal hypoxia preconditioning applied to stem cells have shown to activate protective signals including hypoxia-inducible factor-1 (HIF-1), growth factors, Akt, and ERK signals to further enhance their resistance to apoptosis/necrosis cues by increasing survival signals [30]. Dr. Wei's group has performed extensive studies related to hypoxia preconditioning. In these studies they demonstrated that transplantation of hypoxia preconditioning MSCs improves infarcted heart function [38] and ischemic brain function [124] recovery via enhanced survival of implanted cells and angiogenesis. Also they found hypoxic precondition reduced ES-NPCs apoptosis by 40–50 % in serum-free medium via upregulation of erythropoietin (EPO), Bcl-2, and HIF-1alpha [114].

One study from Dr. Yang's group demonstrated that melatonin pretreatment increased MSCs' survival and proangiogenic activity through Erk1/2 signaling pathway [110], which is consistent with other studies that melatonin treatment enhanced adipose-derived mesenchymal stem cells (ADMSCs) survival and therapy for lung ischemia injury [134] and reduced grafted eEPC apoptosis/necrosis as well as increased their outgrowth in injured kidney [87]. For minocycline, Sakata et al. showed that transplantation of minocycline-preconditioned NSCs protected their survival from ischemic reperfusion injury via upregulation of Nrf2 and Nrf2-regulated antioxidant genes, increased their paracrine factors releasing, attenuated infarct size, and improved neurological performance [94], and doxycycline has the similar protective effects [80]. Additionally, low LPS pretreatment was found to protect MSCs against oxidative stress-induced apoptosis and increase cell engraftment after transplantation into ischemic heart [132]. A recent study showed that EPO pretreatment could also suppress MSCs' apoptosis in response to hydrogen peroxide stimuli [25].

9.1.3.3 Biomaterial-Based Method

The development of biomaterials has evolved from the first-generation, material-based approach that focused on mechanical strength, durability, and biocompatibility to the third-generation, bio-functional materials that try to integrate biological cues to modulate cellular functions by modifying with extracellular matrix (ECM) related to signaling molecules. In recent years, biomaterials have been proven to be an effective strategy for regulating cellular behavior, including promoting cell survival, directing cell differentiation. Advances in biomaterials engineering enable promoting grafted cell survival and engraftment and have generated much attention in stroke therapy.

With regard to injecting stem cells which are encapsulated within biomaterials into ischemic brain, the infarct cavity is always an ideal location. First, it is more clinical relevant since the transplantation procedure is not initiated until infarct cav-

Table 9.2 Preconditioning treatment to improve stem cell survival

Triggers	Stem cells involved	Animal model	Stem cell fate	Outcome
Hypoxia	hESCs [155]; MSC [158, 161, 201]; ES-NPCs [195]	Myocardial infarction; MCAO	Increased neural precursor cell survival; engraftment of MSC was increased; cell survival was increased; promoted their survival, migration, and homing to the ischemic brain region; promote transplanted cell survival	Promoted neuronal differentiation; improvement in global, regional, and diastolic left ventricular functions; an increase in angiogenesis, as well as enhanced morphologic and functional benefits of stem cell therapy; reduced infarct volume and improved behavioral recovery; ES-NPCs exhibited extensive neuronal differentiation in the ischemic brain, accelerated and enhanced recovery of sensorimotor function
Anoxia	MSC [172, 199]	Myocardial infarction	Increased cell survival	Increased fractional shortening, ejection fraction, arteriole density and decreased infarct size; increased the capillary density and the fractional shortening and attenuated myocardial fibrosis
Hydrogen sulfide	MSCs [202]	Myocardial infarction	Improved the survival rate of the transplanted MSCs	Reduced the infarct size and increased left ventricular (LV) function
IL-6	NSCs [94]	MCAO	Protected the grafted neural stem cells from ischemic reperfusion injury	Attenuated infarct size, improved neurological performance and angiogenesis
Melatonin	MSCs [181, 194]; ADMSC [205]	MCAO; acute lung ischemia-reperfusion injury; ischemic kidney	Improved survival of MSCs; decreased apoptosis of ADMSC	Reduced infarct volume, enhanced angiogenesis, neurogenesis and functional recovery; protected the lung from ischemic injury; increased survival, paracrine activity, and efficiency of MSCs
Minocycline	NSCs [188]; OPC [190]	MCAO; in vitro	Minocycline preconditioning protected the grafted NSCs from ischemic reperfusion injury; reduced apoptosis in response to OGD	Attenuated infarct size and improved neurological performance
Doxycycline	NSCs [178]	In vitro	Decreased cell death and increased cell viability after oxygen–glucose deprivation–reoxygenation	Showed cryoprotective via induced the expression of Nrf2
BDNF	NSC [186]	MCAO	Promoted cell survival 1 week after transplantation	BDNF pretreatment of NSCs results in higher initial NSC engraftment and survival, increased neuroprotection, and greater functional recovery

ity is formed, which is already 2–3 weeks after the onset of stroke; second, cavity is adjacent to the highly plastic peri-infarct region, and injection of stem cells into the cavity shows to achieve best outcome. Third, injection into the cavity will not damage normal brain tissues. Although directly injecting stem cells into infarct cavity shows its merit in reduced infarct volume, enhanced behavioral recovery, and increased angiogenesis and neurogenesis, low cell survival is still a major problem that hinders its clinical application. For instance, only 8 % of the grafted NSPC transplanted cells survived 4 weeks posttransplantation in Mongolian gerbils after focal ischemia [43]. In another study, approximately 4 % of grafted NPCs survived at 2 weeks posttransplantation [145].

Previous experimental studies showed that using Matrigel, fibrin glue gels, particles, and other scaffolds as matrices could improve the survival of stem cells in the infarct cavity posttransplantation (Table 9.3). Matrigel is an extracellular matrix comprised of ECM proteins and growth factor mixtures, including collagen, laminin, epidermal growth factor (EGF), and fibroblast growth factor 2 (FGF-2). Jin et al. injected NPCs encapsulated with Matrigel into the infarct cavity in both young and aged rats. Compared to control group, more cells were detected at the infarct site, and best functional recovery was achieved in the NPCs+Matrigel group [45, 46]. However, Matrigel is derived from a mouse sarcoma that raises a serious concern for its clinical application.

The functions of biodegradable polymers such as PGA and PLGA are also extensively investigated in stem cell-based therapy in stroke. For instance, Park et al. implanted NSCs seeded on polyglycolic acid (PGA), a high biocompatible scaffold into the infarct cavity, and found infarct volume was greatly reduced as well as establishment of neuronal connections between exogenous transplanted NSCs and endogenous neurons [85]. Modo's group demonstrated PLGA could act as a structural support for NSCs in infarct cavity to improve cell survival and function [7]. In their further study, they loaded VEGF into the PLGA microparticles and transplanted NSCs which were seeded on the VEGF-releasing PLGA particles into the cavity. Their results showed that VEGF-releasing PLGA not only provides structural support but also attracts ECs into the cavity to induce neurovascular formation [8].

Hyaluronan (HA), a glycosaminoglycan that naturally and abundantly exist in the brain, could involve in brain development and influence cell adhesion, migration, angiogenesis, and axon growth. Thus it is reasonable to choose HA as protective matrices to encapsulate cells for transplantation into the brain to maintain a hydrated and porous environment [83]. Recently, experimental studies from Dr. Thomas Carmichael's group proved that hydrogel composed of cross-linked hyaluronan and heparin sulfate significantly promoted NPCs' survival after transplantation into the infarct cavity, accompanied by reduced inflammation [145]. In their further study, they proposed to modify hyaluronic acid hydrogel with cell adhesion peptide RGD and cross-linked with either MMP degradable peptides or non-MMP degradable peptides through a Michael Addition reaction to produce two hydrogel formulations with two different stiffness moduli (300 Pa in MMP HA and 1000 Pa in non-MMP HA). NPCs derived from induced pluripotent stem cells (iPS-NPC) were encapsulated in the hydrogel matrix and delivered to the infarct cavity of stroke

Table 9.3 Enhancement of stem cell survival by biomaterials

Biomaterials	Stem cells involved	Animal model	Stem cell fate	Outcome
PLGA microparticles [147]	MHP36 cells	MCAO	Cell survival was increased, and cells were differentiated into neurons	PLGA microparticles acted as a structural support for NSCs;
PLGA microparticles loaded with VEGF [148]	hNSCs			NSCs showed neuronal differentiation, and neurovascular unit was performed in the infarct cavity
Matrigel [45, 162]	Human fetal NPCs	MCAO	Enhance the survival of transplanted NPCs	Behavioral recovery was improved, and infarct volume was reduced
Collagen [135, 167, 187, 203]	Cardiomyoblasts	Myocardial infarction	Enhanced early survival of H9c2 cardiomyoblasts after transplantation into ischemic hearts	Left ventricular function was improved
	NSCs	MCAO	Increased cell survival and distribution	Reduced infarct volume, induced angiogenesis
	Marrow stromal cell-derived NPCs;	Excisional wound healing model	Remained longer viability	Improved motor behavior;
	BM-MSCs			significantly enhanced angiogenesis and VEGF
Hyaluronan [168, 183]	NPCs; iPS-NSCs	MCAO	Promoted NPCs' survival and neuronal differentiation after transplantation into the infarct cavity	Enhanced neurovascular unit formation and reduced inflammation
Fibrin glue [151]	iPS	MCAO	N/A	Improved the motor function, reduced infarct size, attenuated inflammation cytokines, and mediated neuroprotection
Collagen with bFGF in gelatin microspheres [179]	NS-MSCs	MCAO	Increased cell survival and proliferation	Significantly improved histological and
				Functional recovery in the rat stroke model

mice. They found that hydrogel system with MMP and RGD modification promoted neuronal differentiation of iPS-NPC and induced minimum inflammation [58].

9.1.4 Bone Marrow Stem Cell Mobilization in Stroke

9.1.4.1 Factors Mediating BMSC Homing

Migration and homing of administered cells to the ischemic regions are clinically relevant and very critical to their therapeutic efficacy. A detailed analysis of the biological responses to brain injury would not only give us insight into the mechanism of stem cell homing but also give us important clues about how we can improve their homing capacity. Now it is clear that following brain injury, homing molecular cues, including chemokines, growth factors, and adhesion molecules, originating from the inflammatory zone in the injured brain, are activated and upregulated to cause BMSC homing. Chemokines such as G-CSF and SDF-1 have been demonstrated to be an important stem cell homing mediator that mobilizes stem cells from bone marrow into the PB. G-CSF treatment enhances tissue regeneration and improves recovery after stroke by mobilizing BMSCs from bone marrow into peripheral blood [91]. Previous studies showed that subcutaneous injection of G-CSF for 5 days after cerebral ischemia promotes BMSC migration to the lesion area, reduces infarcts, and enhances functional recovery in stroke rats [101]. G-CSF treatment is also demonstrated to facilitate neurogenesis in SVZ by increasing the infiltration of BMSC into the brain [99]. BMSCs exert their benefits on cerebral ischemic injuries through promoting neuronal repair and recovery of brain function, which provides a basis for the development of a noninvasive autologous therapy for cerebral ischemia. Some pilot clinical trials demonstrated that G-CSF could mobilize BMSCs in patients after acute stroke safely and provide better neurological outcome compared to conventional treatment [101].

SDF-1 is another important homing factor, which is secreted primarily by bone marrow fibroblasts and is required for BMSC homing/retention in the bone marrow microenvironment. SDF-1 and its receptors CXCR4 and CXCR7 were found upregulated after early focal cerebral ischemia [121] and showed beneficial for the adhesion and migration of BMSCs both to bone marrow and to ischemic tissue through activation of specific integrin molecules. Given that CXCR4 and CXCR7 are present on bone marrow stem cells [14], upregulation of SDF-1 in the local ischemic damage after injury may be related to stem cell homing and engraftment toward the injured tissue. During cerebral ischemia, SDF-1 was found primarily co-localized with endothelial cells and closely interacted with infiltrated BMSCs from bone marrow in the ischemic penumbra region, suggesting that SDF-1 may mediate trafficking of transplanted BMSCs to ischemically damaged tissue. Indeed, overexpression of SDF-1 in ischemic tissues has recently been found to augment EPC-induced vasculogenesis in hind-limb ischemic mice, as well as enhanced recovery of blood perfusion, increased capillary density, and induced partial incorporation of EPCs

into the microvessels [129]. Our previous studies have highlighted biphasic function of SDF-1 in stroke mice in a time-dependent manner. One study demonstrated that injection of CXCR4 inhibitor AMD3100 into ischemic mice during acute phase significantly suppressed inflammatory response and reduced blood–brain barrier disruption via inhibiting leukocyte migration and infiltration [39]; however, another study showed that overexpression of SDF-1 in mice brain during post-acute phase promoted neurovascular recovery, neurogenesis, and angiogenesis through enhancing migration of neural progenitor cells and endothelial cells, while AMD3100 reversed protective effects of SDF-1 [66].

In addition to chemokines, growth factors, inflammatory cytokines, and adhesion-related molecules also play important roles in stem cell homing. For instance, PDGF and VEGF are demonstrated to act as chemoattractants to induce migration of MSCs [105]; IL-6, (TGF)-β1, interleukin (IL)-1β, and tumor necrosis factor (TNF)-α stimulate chemotactic migration through matrix metalloproteinases (MMPs) secreted by the MSCs [18]. During the transmigration process of MSCs through the vascular endothelium, integrins and adhesion molecules are involved. Based on the fact that MSCs express α4β1 integrin and vascular cell adhesion molecule-1 (VCAM-1), it is proposed that MSCs roll along the vascular endothelium may share the same mechanism as white blood cells and HSCs to move through the blood vessels. Indeed, Ip et al. identified that β1 integrins are important for the intramyocardial traffic of MSCs by developing a functional genomics approach [42]. Moreover, the adhesion of rat MSCs to endothelial cells of microvessels is reduced by anti-VCAM-1 antibody [98].

9.1.4.2 Tracking of Grafted Stem Cells In Vivo

Different administration routes will result in different homing, distribution, and engraftment. Experimental studies demonstrated that intracerebral [], intra-arterial, intravenous, and intracisternal injection of MSCs result in reduced infarct volume and enhanced behavioral functional recovery, irrespective of pros and cons existing in each injection method [112]. Intracerebral injection delivers and had the highest cell retention in a desired location compared to other methods [111], but it also induces adverse effects involving seizures and transient motor function impairment given its invasive procedure. Intraventricular transplantation is less invasive but achieves less therapeutic efficacy as intraventricularly injected human NSCs into ischemic rat brain did not show improvement [102]. Intravenous delivery is safer and more feasible, but only few cells could localize to the infarct region [111]. Intra-arterial administration contributes to more cells retaining in the brain than intravenous delivery and is beneficial for behavioral recovery [63]. However, intra-arterial transplantation leads to high mortality (about 40 %) and morbidity due to cell accumulation and microemboli, especially when large-sized stem cells (e.g., MSCs) were transplanted intra-arterially [44], which is a major concern for its clinical translation.

In order to determine stem cell migration and in vivo distribution, noninvasive and real-time imaging modalities are developed in recent years. Several multifunctional nanoprobes with high MR sensitivity are developed by our group to label stem cells and allow us to longitudinally track them after injection by MRI in terms of its high spatial resolution. In one study we labeled MSCs [122] and NSCs [142] with high MR sensitivity fluorescent-magnetite-nanocluster (FMNC) and tracked them by MRI and fluorescent imaging after injection into the contralateral hemisphere of the ischemic mice brain. MSCs were detected to migrate toward the perifocal region of the ipsilateral hemisphere through the corpus callosum. We further developed a trifunctional nanoprobe by adding iodine-125 to superparamagnetic iron oxide nanoparticles, which allows us to quantitatively track MSCs injected into the brain by micro-SPECT/CT and MRI. Using this method we found 30 % of intracerebrally grafted MSCs migrated from the injection hemisphere to the lesion area, and intravenously injection induced more than 90 % of MSCs migrated and accumulated in the lung, while no cells were found in the brain (Fig. 9.1) [111]. However, one major limitation of SPIO-based imaging strategy is that survival and dead cells cannot be distinguished. Signals from survival and dead cells are all captured by MRI and micro-SPECT. To resolve this problem, bioluminescence imaging (BLI) is developed and widely used to track the migration and survival of transplanted cells which are modified with a firefly or Renilla luciferase (Luc) enzyme [143]. However, the spatial resolution and the penetration depth of BLI are limited, which hinder its clinical application at current stage.

Recently, radionuclide probes for PET imaging were designed, as 18F-fluorodeoxyglucose ([18F]-FDG) is the most popular one. Several studies have reported direct imaging of transplanted cells with 18F-FDG [9, 113]. To track survival of grafted cells, the herpes simplex virus type 1-derived thymidine kinase (HSV-1-tk), which could exclusively phosphorylate substrates composed of acycloguanosines, is employed and routinely used to monitor human ESCs and C17.2 NSCs in the rodent brain [106, 118].

9.1.5 Strategies to Improve Bone Marrow Stem Cell Homing

Stem cell homing is a multistep process involving cell attachment, adhesion to the vascular endothelium, and migration through the tissue stromal, which are mediated by different factors, including chemokines, growth factors, integrins, and adhesion molecules. Understanding the mechanism of homing could help us to develop novel strategies to improve their homing ability and further increase the therapeutic efficacy. In principle, those methods that used to increase stem cell survival could also apply to improving stem cell homing.

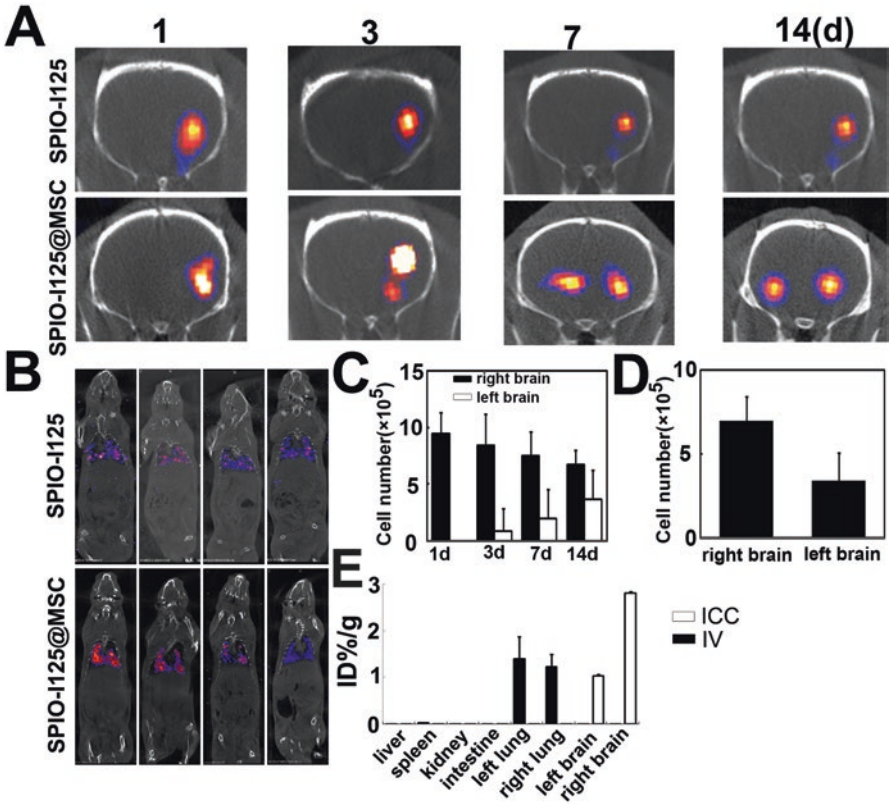

Fig. 9.1 SPECT/CT tracking of (125) I-fSiO4@SPIO-labeled MSCs in ischemic rats after IC and IV injection. (**a**, **b**) SPECT/CT imaging of labeled MSCs and particles alone in ischemic rats after IC (**a**) and IV injection (**b**). (**c**) The radioactivity detected in the right and left hemispheres accounting for the total transplanted dose at different time points after IC injection. (**d**) Ex vivo analysis of radioactivity in right and left hemispheres accounting for the total transplanted dose 14 days after IC injection. (**e**) Biodistribution of (125) I-fSiO4@SPIO-labeled MSCs at 14 days after IV or IC transplantation (Reprinted from Tang et al. [111], Copyright 2015, with permission from Wiley)

9.1.5.1 Homing Gene-Based Method

We and others demonstrated that genetic modification of the target tissue or the stem cells with homing genes is feasible to stimulate their homing ability and further improve behavioral recovery after stroke (Table 9.4). By stereotactic injection of adeno-associated virus (AAV) carrying SDF-1α gene into ischemic mice brain, Li et al. found that migration of endogenous neural stem cells and OPCs from subventricular zone to the peri-infarct region was enhanced and induced increased neurogenesis and oligodendrogenesis, reduced brain atrophy, as well as improved white matter and behavioral recovery [66, 69].

Table 9.4 Enhancement of stem cell homing by gene modification

Overexpressing genes	Stem cells	Animal model	Outcome
CXCR4 [207]	MSCs	Myocardial Infarction	Increased accumulation of BMSCs in the lesion area and an improvement in cardiac function
CCR1 [159]	MSC	Myocardium infarct	CCR1-MSCs accumulated in the infarcted myocardium at significantly higher levels. CCR1-MSC-injected hearts exhibited a significant reduction in infarct size, reduced cardiomyocyte apoptosis, and increased capillary density
ACE2 [150]	EPC	Cerebral ischemia	ACE2 overexpression improved the abilities of EPC migration and tube formation, reduced cerebral infarct volume and neurologic deficits, increased cerebral microvascular density and angiogenesis
HGF siRNA [149]	ASC	Hind-limb ischemia	Transduced ASC-shHGF secreted >80 % less HGF, which led to a reduced ability to promote survival, proliferation, and migration of mature and progenitor endothelial cells in vitro
IGF-1 [156]	MSC	Permanent coronary artery occlusion	IGF-1 transgene expression induced massive stem cell mobilization via SDF-1α signaling and culminated in extensive angiomyogenesis in the infarcted heart
GDNF [163]	NPC	Stroke	More NSPC-GDNF cells migrated toward the ischemic core, reduced infarct volume, and improved behavioral recovery
SCF [193]	NSPCs	Normal mice	Recombinant SCF induces potent NSPC migration in vitro and in vivo through the activation of c-kit on NSPCs
MicroRNA 9 [153]	hESC-derived neural progenitors	Stroke	hNPCs without miR-9 activity also showed enhanced migration

In addition to SDF-1 α, Yu and coworkers demonstrated its receptor CXCR4 also plays a pivotal role in stem cell homing. By transducing MSCs with CXCR4 by lentivirus and injecting them via the femoral vein following MCAO, they found that CXCR4 overexpression promoted MSCs' migration to the infarct region and enhanced neuroprotection via increased angiogenesis [137]. Besides stroke, MSCs overexpressing CXCR4 was also proved to migrate into the cardiac infarct area in a cardiac infarct animal model, leading to a significant improvement in cardiac func-

tion [17]. Additionally, growth factors also show their capacity to enhance stem cell migration posttransplantation. Haider et al. demonstrated that IGF-1 overexpression promoted MSC recruitment through paracrine activation of SDF-1α and enhanced myocardial repair [31]. When NPCs overexpressing GDNF were injected into ischemic rat brain, more cells were found accumulated in the lesion area [49]. For EPC it was reported that overexpression of angiotensin-converting enzyme 2 (ACE2) improved the EPC migration and tube formation, and injection of lentivirus-ACE2-transfected EPCs reduced cerebral infarct volume and neurological deficits, which was driven by eNOS [16].

Recently, miRNAs were demonstrated to play an important role in stem cell migration. One study from Delaloy et al. for the first time identified miR-9 as a novel regulator that coordinates the proliferation and migration of hNPCs. They found that hNPCs without miR-9 activity showed enhanced migration when transplanted into mouse embryonic or adult brains in a stroke mouse model [21]. Other miRNAs such as miR-10b and miR-204 have been also proven to play an important role in cell migration [41, 72].

9.1.5.2 Preconditioning-Based Method

As we discussed above, although overexpression of homing genes in both grafted stem cells and local brain tissues improves stem cell homing, several disadvantages exist in this strategy. For instance, uncontrolled expression of introducing genes raises the safety issue, and the risk of tumorigenicity such as leukemia also limits its application. Recently, upregulation of homing genes in MSCs under stress conditions including hypoxia has been confirmed, which may be mediated by HIF-1 alpha [24]. It is reported that hypoxia induces CXCR4 and CXCR7 expression in BMSCs via upregulated HIF-1α [75], and hypoxia preconditioning enhances migration of MSCs via increased expression of cMet [93], which hints at the possibility that hypoxia preconditioning could enhance mobilization of stem cells to lesion sites in ischemic brain. In addition to hypoxia preconditioning, H2O2 preconditioning could increase the migration of MSCs through upregulation of CXCR4 and activation of extracellular signal-regulated kinase (ERK) [65], and pretreatment of HSCs with SDF-1 or dextran sulfate enhances their homing to bone marrow, which is involved in several genes including CXCR4 and MMP-9 [33].

Accumulating evidence shows that pretreatment with growth factors also increases MSCs' mobilization (Table 9.5). In previous investigations, IGF-1 as well as VEGF increased MSC migratory responses via CXCR4 chemokine receptor signaling which is PI3/Akt dependent [70, 109]. Early studies have demonstrated that statins increased EPC number and function through activating the Akt/eNOS pathway [22]. Likewise, enhancement of eNOS enhancers improves the stem cell homing. In particular, pretreatment with eNOS enhancers significantly increased the homing of the intravenously infused EPCs or BMCs and led to increased exercise capacity in a hind-limb ischemia model [95].

Table 9.5 Preconditioning mediators to enhance stem cell homing

Triggers	Stem cells involved	Animal model	Stem cell fate	Outcome
Hypoxia	hESCs [155] MSC [158, 161, 201]; ES-NPCs [195]	Myocardial infarction; MCAO	Increased neural precursor cell survival; engraftment of MSC was increased; cell survival was increased; promoted their survival, migration, and homing to the ischemic brain region; promote transplanted cell survival	Promoted neuronal differentiation; improvement in global, regional, and diastolic left ventricular functions; an increase in angiogenesis, as well as enhanced morphologic and functional benefits of stem cell therapy; reduced infarct volume and improved behavioral recovery; ES-NPCs exhibited extensive neuronal differentiation in the ischemic brain, accelerated and enhanced recovery of sensorimotor function
H2O2	MSC [172, 199]	Myocardial infarction	Increased cell survival	Increased fractional shortening, ejection fraction, arteriole density and decreased infarct size; increased the capillary density and the fractional shortening and attenuated myocardial fibrosis
Hydrogen sulfide	MSCs [202]	Myocardial infarction	Improved the survival rate of the transplanted MSCs	Reduced the infarct size and increased left ventricular (LV) function
IGF-1	NSCs [94]	MCAO	Protected the grafted neural stem cells from ischemic reperfusion injury	Attenuated infarct size, improved neurological performance and angiogenesis
VEGF	MSCs [181, 194]; ADMSC [205]	MCAO; acute lung ischemia-reperfusion injury; ischemic kidney	Improved survival of MSCs; decreased apoptosis of ADMSC	Reduced infarct volume, enhanced angiogenesis, neurogenesis, and functional recovery; protected the lung from ischemic injury; increased survival, paracrine activity, and efficiency of MSCs
Minocycline	NSCs [188]; OPC [190]	MCAO; in vitro	Minocycline preconditioning protected the grafted NSCs from ischemic reperfusion injury; reduced apoptosis in response to OGD	Attenuated infarct size and improved neurological performance

(continued)

Table 9.5 (continued)

Triggers	Stem cells involved	Animal model	Stem cell fate	Outcome
Doxycycline	NSCs [178]	In vitro	Decreased cell death and increased cell viability after oxygen–glucose deprivation–reoxygenation	Showed cryoprotective via induced the expression of Nrf2
BDNF	NSC [186]	MCAO	Promoted cell survival 1 week after transplantation	BDNF pretreatment of NSCs results in higher initial NSC engraftment and survival, increased neuroprotection, and greater functional recovery
Valporate and lithium [198]	MSC	MCAO	Priming with VPA or lithium increased the number of MSC homing to the cerebral infarcted regions, and copriming with VPA and lithium further enhanced this effect through VPA-induced CXCR4 overexpression and lithium-induced MMP-9 upregulation	Priming with VPA and/or lithium improved functional recovery, reduced brain infarct volume, and enhanced angiogenesis

9.1.5.3 Biomaterial-Based Method

With the rapid development of tissue engineering, many state-of-the-art biomaterials have been developed to combine stem cells to treat cerebrovascular diseases, with the ultimate goal of repairing organs and tissue. In past two decades, many protein-based, polysaccharide-based, polymer-based, peptide-based, and ceramic-based scaffolds that have been proven to promote the viability, differentiation, and migration of stem cells are well designed [125]. Both natural and synthetic biomaterials have been developed and combined with stem cell-based therapy to promote cell survival and migration posttransplantation (Table 9.6).

Fibrin gel is ranked as the first biomaterial to prevent bleeding and promote wound healing in terms of the abundance of fibrinogen, ease fabrication, controllable gelation time, and tunable mechanical property. Fibrin gel is able to exclusively enhance the migration of the transplanted cells toward the lesion boundary zone, even it disappears completely 4 weeks after transplantation [133]. In one study performed by Lee and coworkers, they designed a VEGF-releasing gel that could attract NSC migration [171]. It is also reported that PEGylated fibrin patch controlled the release of SDF-1α at the infarct site and increased the rate of c-kit+ stem

Table 9.6 Biomaterial-based method to enhance stem cell homing

Biomaterials	Stem cells/ homing factors involved	Animal model	Stem cell fate
Fibrin gel	BMSC [204]	Cortical injury	Fibrin matrix enhanced the retention of the transplanted cells within the lesion, migration toward the lesion boundary zone, and differentiation into the neurons and perivascular cells
	C17.2 cell line [171]	Myocardial ischemia	The cells migrated toward the fibrin gel, with the total migration distance of 102.4 ± 76.1 μm over 3 days
	(PEGylated) fibrin patch [208]		The myocardial recruitment of c-kit+ cells was significantly higher in the group treated with the SDF-1a PEGylated fibrin patch
Alginate microspheres	Bone marrow-derived progenitor cells [165]	Hind-limb ischemia	Increased mobilization of bone marrow-derived progenitor cells and also improved recruitment of angiogenic cells expressing CXCR4 from bone marrow and local tissue
	hMSCs [206]	Myocardial ischemia	RGD-modified alginate improved cell attachment and growth and increased angiogenic growth factor expression
starPEG-heparin hydrogels	EPCs [146]	In vitro	Higher migration rates were achieved
Gtn-HPA hydrogels and PCNs	NPCs [174]	In vitro	Gtn-HPA/SDF-1-PCN hydrogels promoted hemotactic recruitment to enhance infiltration of aNPCs by 3- to 45-fold relative to hydrogels that lacked SDF-1
Collagen microgel	hMSCs [197]	Hind-limb ischemia	Optimized hMSC embedded microgels were shown to induce vascular repair and functional improvement by increasing SDF-1 expression
HA	EPCs [177]	Myocardial ischemia	Induced continuous homing of EPCs and improved left ventricular function in a rat model of myocardial infarction
	SDF-1 [191]		Injection of biomimetic hydrogels containing SDF-1 and Ac-SDKP increased stem cell homing and significantly improved left ventricle function, increased angiogenesis, decreased infarct size and great

(continued)

Table 9.6 (continued)

Biomaterials	Stem cells/ homing factors involved	Animal model	Stem cell fate
PLGA	SDF-1 [152, 196]	In vitro	Released SDF-1α caused significant migration of MSCs throughout the duration of release from the microspheres
			Threefold increase of the host-derived stem cell migration at the interface for up to 2 weeks
PCL	MSCs [189]	Bone tissue engineering model	MSCs were shown to migrate within a polycaprolactone scaffold in response to SDF-1
PLEOF [157]	BMSCs	In vitro	The migration of BMS cells in response to time-released SDF-1alpha closely followed the protein release kinetics from the hydrogels
PUASM [164]	SDF-1	MCAO	Systemic administration of SDF-1α-loaded copolymer into ischemic rat resulted in enhanced angiogenesis and neurogenesis
SPIONs combined with exterior magnet	EPCs [173]	MCAO	SPION-labeled EPC homing was greatly increased in ischemic hemisphere with magnetic field treatment
	MSCs [185]	Balloon angioplasty in a rabbit model	Magnetic targeting of mesenchymal stem cells gives rise to a sixfold increase in cell retention following balloon angioplasty in a rabbit model
	hNSCs [192]		Magnet treated rats had a larger number and greater distribution of ferumoxide-labeled NSCs as compared with controls

cell recruitment and offered potential therapeutic benefits in the myocardium ischemic mice [140]. This body of work suggests that migration of stem cells can be monitored by fibrin scaffolds.

Recently, scaffolds fabricated from gelatin [130], collagen [88], alginate [36], and hyaluronic acid (HA) [128] have been developed for the controlled release of growth factors, which could provide homing signals to enhance stem cell migration. Kuraitis et al. found encapsulating SDF-1 into alginate microspheres led to increased mobilization of bone marrow-derived CXCR4+ progenitor cells and restoring perfusion to ischemic tissues via neovascularization [56]. Further studies demonstrated hMSCs encapsulated in RGD-modified alginate microspheres are capable of facilitating myocardial repair [135]. Baumann et al. reported that encapsulating SDF-1α with starPEG-heparin hydrogels enhanced migration of EPCs in vitro [6]. Lim et al.

developed a multifunctional biomaterial comprising injectable gelatin-hydroxyphenylpropionic acid (Gtn-HPA) hydrogels and dextran sulfate/chitosan polyelectrolyte complex nanoparticles (PCNs) to carry SDF-1 to promote infiltration of NPCs through MMP-9 [73]. In particular, an interesting study fabricated and optimized a shape-controlled 3D type-I collagen-based microgel platform to modulate SDF-1 expression of hMSCs, and hMSCs embedded in the microgels were shown to induce vascular repair and functional improvement in hind-limb ischemic mouse [116]. Currently, HA is gaining its popularity as a biomaterial for tissue regeneration [62]. By chemically modifying HA with hydroxyethyl methacrylate, controlled release of SDF-1 was achieved after its encapsulation into HA, and enhanced endothelial progenitor cell chemotaxis was identified [79]. It is also reported that loading SDF-1 and angiogenic peptides (Ac-SDKP) to HA-based hydrogel promoted regeneration of cardiac function through increasing stem cell homing and angiogenesis [103].

Poly lactic-co-glycolic acid (PLGA) is an FDA-approved polymer and the most attractive polymeric drug/protein carrier among those synthetic materials as its high biocompatibility, biodegradability, and tunable mechanical property. PLGA has been extensively designed for controlled release of small molecule drugs, proteins, and other macromolecules in commercial use and in research. Double-emulsion solvent extraction/evaporation is a routine technique to load proteins to biodegradable PLGA microspheres. Using this strategy, Cross et al. loaded SDF-lα into PLGA microspheres for releasing SDF-1α over 50 days without affecting its bioactivity, and significant migration of MSCs throughout the duration of release from the microspheres was observed [19]. Thevenot and colleagues fabricated PLGA salt-leached scaffolds to carry SDF-1 and implanted in the subcutaneous cavity of Balb/c mice. They found this strategy enhanced host-derived stem cell engraftment by threefold compared to conventional mini-osmotic pump delivery for up to 2 weeks with limited inflammatory response [115].

In addition to PLGA, polycaprolactone (PCL) and poly (lactide ethylene oxide fumarate) hydrogel (PLEOF) have also been used to achieve MSC recruitment. Schantz et al. have developed acellular PCL scaffolds that allowed sequential delivery of VEGF, SDF-1, and bone morphogenetic protein-6 (BMP-6) in the rat and increased MSCs infiltrating into the scaffold, with concomitant angiogenesis [97]. In another study, He et al. synthesized SDF-1-loaded PLEOF hydrogel with poly(l-lactide) (PLA) fractions. A pronounced burst release followed by a period of sustained release was achieved, and MSCs showed migration to SDF-1 in a dose-dependent manner [34]. Recently, Kim et al. synthesized a dual pH-sensitive copolymer-poly (urethane amino sulfamethazine) (PUASM)-based random copolymer for controlled release of SDF-1 in stroke. This copolymer showed high protein encapsulation efficiency at pH 7.4, and at pH 5.5, it could release protein rapidly. Systemic administration of SDF-1α-loaded copolymer into ischemic rat resulted in enhanced angiogenesis and neurogenesis [51].

Recent studies have highlighted the role of superparamagnetic iron oxide nanoparticles in targeted cell delivery. Experimental studies from Dr. Yang's lab showed that intravenous injection of SPION-labeled EPCs into ischemic mice and

followed by magnetic field treatment promoted their migration to the infarcts, further reduced brain atrophic volume, and improved neurobehavioral outcomes [64]. Other studies with this method also showed that magnetic targeting of MSCs or hNSCs led to increased cell retention following their injection [92, 104]. An interesting study reported that small direct current (DC) electric fields induced significant directional migration of hNSCs toward the cathode independent of CXCR4 signal [27].

9.2 Conclusion

Bone marrow-derived stem cells have been demonstrated as promising sources of adult stem cells for regeneration and repair of neurological disorders, including ischemic stroke. On the other hand, many experimental studies make us recognize many fundamental questions related to the cell survival, homing, and engraftment that contribute to the limited efficacy of BM-derived stem cell transplantation in the clinic. We and other groups have proposed many strategies such as gene modification, preconditioning treatment, and biomaterial-based method to overcome these limitations. Strategies to improve cell survival and homing would enhance their therapeutic efficacy and strengthen the application potential of stem cell therapy. In summary, stem cell-based therapy for ischemic stroke in humans is still in its infancy. Further basic and translational studies are required before it becomes a scientifically proven strategy in clinical setting.

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