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REVIEW ARTICLE

Neovascularization and tissue regeneration by endothelial progenitor cells in ischemic stroke

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Abstract

Endothelial progenitor cells (EPCs) are immature endothelial cells (ECs) capable of proliferating and differentiating into mature ECs. These progenitor cells migrate from bone marrow (BM) after vascular injury to ischemic areas, where they participate in the repair of injured endothelium and new blood vessel formation. EPCs also secrete a series of protective cytokines and growth factors that support cell survival and tissue regeneration. Thus, EPCs provide novel and promising potential therapies to treat vascular disease, including ischemic stroke. However, EPCs are tightly regulated during the process of vascular repair and regeneration by numerous endogenous cytokines that are associated closely with the therapeutic efficacy of the progenitor cells. The regenerative capacity of EPCs also is affected by a range of exogenous factors and drugs as well as vascular risk factors. Understanding the functional properties of EPCs and the factors related to their regenerative capacity will facilitate better use of these progenitor cells in treating vascular disease. Here, we review the current knowledge of EPCs in cerebral neovascularization and tissue regeneration after cerebral ischemia and the factors associated with their regenerative function to better understand the underlying mechanisms and provide more effective strategies for the use of EPCs in treating ischemic stroke.

Keywords Endothelial progenitor cells · Ischemic stroke · Neovascularization · Neurogenesis · Stromal cell-derived factor-1

Abbreviations

EPCs	Endothelial progenitor cells
BM	Bone marrow
ECs	Endothelial cells
rtPA	Recombinant tissue plasminogen activator
SDF-1	Stromal cell-derived factor-1
VEGF	Vascular endothelial growth factor
VEGFR-2	Vascular endothelial growth factor receptor-2
IGF-1	Insulin-like growth factor-1
MMP-9	Matrix metalloproteinase-9
G-CSF	Granulocyte colony stimulating factor
VCAM-1	Vascular cell adhesion molecule-1
HIF-1	Hypoxia-inducible factor-1
PSGL-1	P selectin glycoprotein ligand-1
ICAM-1	Intercellular adhesion molecule-1
MCAO	Middle cerebral artery occlusion

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Introduction

Stroke is a major cause of death and adult disability worldwide, of which 87% is ischemia [1]. Reperfusion therapy has been emphasized for the treatment of ischemic stroke, including intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) within 4.5 to 9 h and endovascular intervention with mechanical thrombectomy for large artery occlusion within 6 to 24 h of stroke symptom onset [2, 3]. Although these treatment options are effective for acute ischemic stroke, many patients do not received thrombolytic therapy after an ischemic episode due to the narrow therapeutic time window and other factors such as limited economic conditions and medical resources [3]. The functional recovery from ischemic stroke for patients who are unable to receive intravenous rtPA or mechanical thrombectomy depends primarily on effective revascularization and

restoration of blood supply in the ischemic tissues. Endothelial progenitor cells (EPCs) are bone marrow (BM)-derived immature endothelial cells that migrate into the peripheral circulation and locate into the ischemic regions in response to injury stress [4]. EPCs have the potential to proliferate and differentiate into mature endothelial cells (ECs) to repair damaged endothelium, form new blood vessels, and secrete various cytokines and growth factors to provide protective support for the repair of injured tissue [5]. Multiple studies have confirmed that the role of EPCs in the recovery following cerebral ischemic injury, and the increased numbers of progenitor cells in the bloodstream are closely associated with a better outcome after cerebral ischemia [6]. Thus, EPCs provide a novel and promising potential treatment for ischemic stroke and a predictive biomarker for cerebrovascular risk and vascular function [7]. The therapeutic effects of EPCs on cerebral ischemia depend on their number and functional activities, which are regulated by several factors, including endogenous and exogenous cytokines and drugs [8]. Vascular risk factors such as hypertension, diabetes, hypercholesterolemia, smoking, and high homocysteine (Hcy) also impair EPC functions including mobilization, migration, proliferation, and differentiation, and ultimately decrease their therapeutic efficacy after ischemic injury [9–12]. Therefore, the regenerative capacity of EPCs needs to be considered during the treatment of ischemic injury, especially under pathogenic conditions. This article reviewed the current knowledge of EPCs involvement in neovascularization and tissue repair after cerebral ischemia, including mechanisms of progenitor cell mobilization, recruitment and adhesion, and the association among various factors that influence the functional capacity of EPCs.

Ischemic stroke

Ischemic stroke is a cerebral anoxic lesion and necrosis disorder caused by blockage of local blood supply in regions of cerebrum, resulting in a corresponding loss of neurological function. The clinical outcome and recovery of cerebral infarction are closely related to the extent of blood flow reduction and duration of the ischemic period [13]. The optimal therapeutic method for acute ischemic stroke patients is reperfusion therapy, including intravenous thrombolysis with rtPA to dissolve the thrombus and endovascular intervention with mechanical thrombectomy to recanalize the occluded artery [14, 15]. However, the narrow therapeutic time window of 4.5 h for rtPA in patients with ischemic stroke or patients with a mismatch of CT or MRI core/perfusion within 4.5 to 9 h of stroke symptom onset restricts its administration [3]. Intravenous rtPA also has limited efficacy in dissolving clots containing calcium and cholesterol crystals, such as old and large clots. Endovascular therapy provides an alternative method to remove clots that are resistant to enzymatic degeneration or to recanalize large vessels that are occluded, and clinical data has highlighted the benefit of mechanical thrombectomy for an extended time window of 6 to 24 h after the onset of the ischemic injury [14, 16]. Although mechanical thrombectomy has been confirmed to be an effective intervention, most acute ischemic stroke patients do not receive the treatment after the onset of ischemic injury due to a shortage of neurointerventionists, the high costs, and delay in arriving at a hospital [3].

Pathologically, ischemic regions include an infarct core and peri-infarct penumbra area. Neural cell death is inevitable in the ischemic core, but it is possible to rescue cells in the ischemic penumbra that contains viable tissue. Preventing the death of vulnerable neural cells in penumbra is critical for functional brain recovery after cerebral infarction [17]. Reconstruction of blood vessels and reestablishment of the local blood supply are critical to deliver oxygen and nutrients to injured tissues for neural repair and recovery, especially for penumbra survival [18, 19].

EPCs are endothelial precursor cells implicated in vascular injury repair and neovascularization [18, 20]. Experimental and clinical studies have demonstrated that following cerebral ischemia, EPCs migrate from the BM into ischemic regions to reconstruct blood vessels to restore the blood supply, promote neural cell survival, and play a crucial role in cerebral recovery after cerebral injury [4, 5, 7, 21]. Therefore, EPCs could provide novel and promising potential therapies for poststroke neovascularization and regeneration.

EPCs in vascular remodeling

The vascular endothelium is a functional and dynamic barrier between the circulating blood and surrounding tissues. The endothelium plays a critical role in maintaining vascular structure and homeostasis and protecting vessels from the invasion of lipids and inflammatory cells and the formation of arterial thromboses. However, the endothelium is exposed to various stimuli originating from the circulating blood, such as hemodynamic forces, drug-related cytotoxicity, and immune responses, and the resulting dysfunction and injury might lead to a range of vascular diseases such as myocardial infarction and ischemic stroke [22]. The vascular risk factors such as hypertension, diabetes, hypercholesterolemia, a high homocysteine (Hcy) level, and smoking also impair vascular endothelial cells [9–12]. Structural damage and impairment of endothelial integrity increase endothelial permeability to lipoproteins and inflammatory cells and ultimately lead the formation of atherosclerosis [23]. Atherosclerosis, especially intracranial atherosclerotic disease,

is recognized as a common cause of ischemic stroke, and endothelial dysfunction plays an essential role in its onset and progression [24]. Maintenance of endothelial integrity requires remodeling and repair of dysfunctional and injured endothelial cells. This process depends on the proliferation and migration of surrounding ECs. Recent evidence suggests that BM-derived EPCs are able to differentiate into ECs and replace the injured endothelium [25]. Hypoxia or signals from the injured tissue mobilize EPCs from the BM to enter the peripheral blood circulation, then direct them to populate to the sites of endothelial denudation. EPCs then differentiate into mature ECs to replace the dysfunctional cells, which helps maintaining endothelial homeostasis and integrity. In addition to directly incorporating into the injured vessels, EPCs secrete a series of cytokines and growth factors, including vascular endothelial growth factor (VEGF), stromal cell-derived factor-1 (SDF-1), and insulin-like growth factor-1 (IGF-1). These secretory factors promote proliferation of resident vascular ECs, enhance further infiltration of BM-derived EPCs into ischemic regions, and provide trophic support for cell survival [5, 18]. Moreover, EPCs express endothelial nitric oxide synthase (eNOS) and upregulate its expression in response to injury stress [26]. EPCs also increase the production of endogenous nitric oxide (NO) in an eNOS-dependent manner [26]. NO participates in the maintenance of vascular integrity through the modulation of platelet-endothelial interactions [27]. Notably, the surrounding mature ECs gradually lose their proliferative capacity after endothelial injury. Thus, the process of reestablishing the endothelium following injury requires EPC mobilization and their integration into the vessels to facilitate repair of the damaged endothelium. Therefore, the circulating levels of EPCs are increasingly considered to be an important biological marker that can be used to predict endothelial dysfunction and cerebrovascular events.

EPC mobilization, recruitment, and adhesion after ischemic stroke

EPCs are quiescently lodged in the stem cell niche in the BM, which provides a supportive microenvironment for the progenitor cells to maintain their bioactivity [28]. Activation and mobilization of EPCs from BM to enter into the peripheral circulation are triggered by a series of cytokines and growth factors released by injured tissues, of which SDF-1 appears to be the most important [29]. Hypoxia-inducible factor-1 (HIF-1) expression levels are increased in ischemic tissue, followed by the production of its downstream factor, SDF-1. SDF-1 induces EPC mobilization into the peripheral circulation through a CXCR-4-dependent mechanism [30]. CXCR-4 is a receptor of SDF-1 that is expressed on the surface of EPCs. The interaction of SDF-1 and CXCR-4 activates matrix metalloproteinase-9 (MMP-9) and the release of sKitL from the stromal cell membrane into the surrounding space. sKitL then binds with c-kit, which also is expressed on the surface of EPCs, and subsequently detaches c-Kit$^+$ EPCs from the cell niche to enter into peripheral circulation [31]. eNOS also is a critical inducer of EPC mobilization. EPCs upregulate eNOS expression during ischemia, which stimulates the progenitor cells to move into the peripheral circulation [32]. Granulocyte colony-stimulating factor (G-CSF) and other cytokines such as VEGF also are involved in EPC mobilization [33]. G-CSF stimulates the degranulation of neutrophils followed by the proteolytic cleavage of vascular cell adhesion molecular-1 (VCAM-1) expressed by BM stromal cells, which results in progenitor cell mobilization [33]. VEGF promotes SDF-1 production, which induces the release of EPCs from the BM into peripheral circulation [34]. Moreover, SDF-1 interacts with other mobilizing factors such as G-CSF to further mobilize EPC movement into the peripheral circulation [35].

The recruitment of circulating EPCs into ischemic regions is necessary for the progenitor cells to execute their repair function, which relies on the chemotactic molecules released by damaged tissues [18]. SDF-1 is a critical homing signal for EPCs, and the levels of SDF-1 in ischemic tissues are in direct proportion to the number of EPCs recruited into the neovascularization sites [36]. After its release, SDF-1 forms a concentration gradient between the peripheral circulation and the injured tissues, which attracts the circulating EPCs into the ischemic areas and facilitates their subsequent adhesion to vessel lesions [37]. Additional evidence demonstrates that SDF-1-induced EPC migration is mediated through the PI3K/Akt/eNOS signal transduction pathway [38]. CXCR7 is another receptor for SDF-1 that is expressed on the EPC surface and is implicated in directing the progenitor cells to move into ischemic tissue [39]. SDF-1/CXCR7 axis also plays a crucial role in the regulation of function and survival of EPCs in pathogenic conditions [40].

The adhesion of EPCs to injured blood vessels and activated ECs relies on the interaction of their surface molecules with corresponding ligands or proteins on the activated ECs and subendothelial matrix [28]. Secreted SDF-1 activates EPCs expressing adhesion molecule p-selection selectin glycoprotein ligand-1 (PSGL-1) on their surface [41]. PSGL-1 interacts with its receptor P-selectin, which is expressed on the activated subendothelium of injured vessels, to facilitate the incorporating of progenitor cells into the injured vessels [37]. E-selectin is another important adhesive molecule involved in EPC migration. Activated ECs increase their expression of E-selectin, a receptor for CD34 that is expressed on the surface of EPCs [42]. The binding of CD34 and E-selectin mediates cell-to-cell contact to enhance EPC migrating into injured vessels and promote their regenerative function [43]. EPCs selectively express

β1- and β2-integrins, which contribute to strengthening the attachment of EPCs to damaged endothelium [44]. After the release of high-mobility group box 1 (HMGB1) by damaged tissue, it binds to its receptors that are expressed on EPCs, which activates β1- and β2-integrins. These activated integrins interact with intercellular adhesion molecule-1 (ICAM-1) that is expressed on ischemic vessels, resulting in EPC movement and invasion into the subendothelium [45]. Moreover, GPIIb-dependent platelet aggregation provides a cross-linking structure that allows EPCs to bind to the sites of vascular injury [41]. α4-integrin also participates in the adhesion of circulating progenitor cells to injured vessels [46]. The recruitment and retention of EPCs into injured tissue allow them to participate in the repair of injured vessels and also in neurogenesis, and are closely associated with the therapeutic efficacy of the progenitor cells.

EPCs in neovascularization and neurogenesis after ischemic stroke

BM-derived EPCs can differentiate into mature vascular endothelial cells in the process of vascular repair and new blood vessel formation. The contributions of EPCs to neovascularization and regenerative repair have been documented in various vascular diseases, including ischemic stroke [47]. Studies in animal models have shown that EPCs travel to sites of arterial injury and increase the blood vessel density in lesions following ischemic stroke [48]. Administration of exogenous EPCs in a rat model of transient middle cerebral artery occlusion (MCAO) increased regional blood flow, reduced infarct volume, and improve functional recovery [49]. Mounting clinical evidence suggests that circulating EPC levels are closely associated with the outcome of patients with acute ischemic stroke [50–52]. Increased expression of EPC regulating factors, such as SDF-1 and VEGF, has been detected in the ischemic penumbra, supporting the involvement of the progenitor cell in cerebral injury repair [37, 53]. EPCs can aid in the recovery and reconstruction of the functions of neural cells after ischemic stroke via several different mechanisms (Fig. 1). EPCs can differentiate into mature ECs to repair injured endothelium and form new blood vessels, which contribute to the restoration of blood flow and provide a nutrient-rich microenvironment for injury recovery [54]. Moreover, following aggregation into ischemic areas, EPCs secrete a series of cytokines such as SDF-1, VEGF, and IGF-1 [5, 18]. These secreted factors create a microenviroment for EPCs to integrate into the damaged vessels, and also contributes to neural survival and regeneration [5]. The secreted factors promote the differentiation of EPCs into mature ECs to replace the dysfunctional or directly integrate into the injured endothelium, and activate local ECs to proliferate and migrate to areas of damaged endothelium to participate in repair [25]. SDF-1 is a chemoattractant that facilitates the migration of immature neural progenitor cells to injured brain regions [55]. Increased levels of SDF-1 in the cortical peri-infarct region after ischemic stroke promote angiogenesis, vasculogenesis, neurogenesis, and ultimately the repair of ischemic brain injury [56]. VEGF contributes to the proliferation and migration of local neural cells and protects cerebral endothelial cells from ischemic-reperfusion injury via the PI3K/Akt pathway [57]. Furthermore, EPCs express eNOS that increases the generation of NO by catalyzing the conversion of L-arginine to L-citrulline [58]. NO is an important vasoprotective factor that is involved in maintaining vascular integrity and blood circulation and preventing the formation and development of thromboses through regulation of the interaction between platelets and the endothelium [8, 27, 59]. EPCs also secrete functional exosomes that contribute to new vessel formation by facilitating the proliferation, migration, and angiogenic function of endothelial cells [60]. These studies have confirmed the integral role of EPCs in vascular repair and neural regeneration after ischemic stroke. However, several components, including vascular risk factors, endogenous and exogenous cytokines, and drugs, affect the quantity and function of EPCs to modulate their ability to repair tissues after cerebral ischemia.

Risk factors for ischemic stroke related to EPC number and function

EPCs participate in repairing damaged endothelium and new blood vessel formation in ischemic tissues, and these functions are associated with the quantity and quality of the progenitor cell. Increased numbers of EPCs in ischemic stroke tissues have been shown to correlate with better outcomes and reductions in infarct volume [20]. However, many risk factors for stroke, such as hypertension, diabetes, hypercholesterolemia, smoking, and high homocysteine (Hcy) levels, impair the capacity of EPCs in mobilization, migration, proliferation, and differentiation. These impairments ultimately reduce the number of EPCs and the ability of the cells in endothelial repair and new blood vessel formation. Hcy is a common pathogenic factor for vascular disease, which accelerates the senescence and apoptosis of EPCs and reduces their ability to proliferate. The underlying mechanisms include diminishing telomerase activity, Akt phosphorylation, activation of caspase-3 and caspase-8, and cytochrome c release; these effects can be partially reversed by administrating vitamin B [9, 61]. Experimental and clinical studies have shown that the number of EPCs is significantly reduced in patients with hypercholesterolemia compared to control subjects, and the functional activities of isolated EPCs, including proliferation, migration, adhesion, and in vitro tube-forming capacity, also are impaired. These

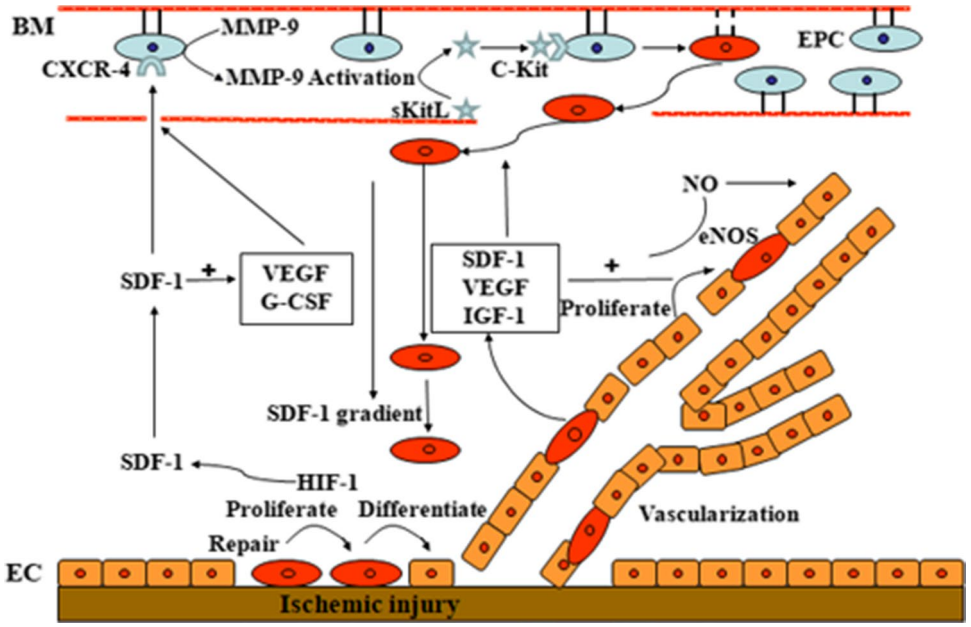

Fig. 1 Vascular repair and neovascularization of EPCs in ischemic stroke. Ischemic injury causes the release of HIF-1, followed by the production of its downstream factor SDF-1. EPCs are mobilized from the BM to enter into the peripheral circulation and are recruited to move along the SDF-1 gradient to enter the ischemic regions. VEGF and other mobilizing factors such as G-CSF contribute to the mobilization of EPCs. SDF-1 also cooperates with other mobilizing factors such as G-CSF to enhance further mobilization of EPCs. The circulating EPCs then move to the ischemic regions, proliferate, and differentiate into mature ECs to replace dysfunctional ECs or directly integrate into the injured endothelium to promote new blood vessel formation. EPCs also promote the recovery of ischemic injury through secretory mechanisms. EPCs secrete several different cytokines, including SDF-1, VEGF, and IGF-1, which create a microenvironment for EPCs to cause further mobilization and localization in the areas of ischemic injury and to increase neural and vascular survival and regeneration. EPCs, endothelial progenitor cells; EC, endothelial cell; HIF-1, hypoxia-inducible factor-1; SDF-1, stromal cell-derived factor-1; VEGF, vascular endothelial growth factor; G-CSF, granulocyte colony stimulating factor; IGF-1, insulin-like growth factor-1

results indicate a novel pathological mechanism of hypercholesterolemia in vascular diseases, since the reduction of EPCs and their decreased functions are associated with impaired vascular remodeling and reconstruction [10]. Hyperglycemia is a common pathogenic factor associated with microvascular and macrovascular diseases. Dysregulation of vascular remodeling and abnormal neovascularization are considered to be central events in the pathogenesis of diabetic vascular complications [62]. EPCs are increasingly recognized as essential components in vascular repair and new blood vessel formation after injury, and their number and functional activities are reduced in diabetes [12]. EPCs from diabetic individuals express low levels of CXCR7, which contributes to impaired adhesion and angiogenic function of the progenitor cells. SDF-1 treatment reverses diabetic EPC dysfunction and improves their movement to ischemic areas and participation in new vessel formation in injured tissues through activation of Nrf2 via the Akt/GSK-3β/Fyn pathway [40]. Similarly, EPCs from hypertensive patients also express decreased levels of CXCR4, and exhibit impaired new blood formation. Upregulation of CXCR7 levels can partially reverse the reduction in functional activities of diabetic or hypertensive EPCs, thus provide a novel therapeutic target for increased endothelial repair capacity under these pathological conditions [11, 40]. Clinical studies have suggested that smoking is associated with reduced numbers of EPCs, and subsequently contributes to vascular dysfunction and vascular disorders [63]. Active smoking impairs EPC mobilization and migratory response, leading to deleterious consequences for functional recovery after ischemic vascular disease. The underlying molecular mechanisms may be associated with the activation of galectin-3 via the AMPK/mTOR signaling pathway [64]. Identification of new strategies to increase EPC numbers and restore their repair function is necessary to improve the therapeutic efficacy of the progenitor cells in ischemic stroke under a range of pathogenic conditions.

Positive factors related to EPC quantity and function

Many different studies have shown that numerous endogenous and exogenous cytokines and drugs increase the mobilization, migration, proliferation, and differentiation of

EPCs, and promote their repair capacity [65, 66]. Erythropoietin (EPO) is shown to protect the brain against ischemic injury by increasing circulating EPCs and subsequent neovascularization and decreasing inflammation and neuronal apoptosis [67]. Compared to controls, EPO therapy in patients after acute ischemic stroke resulted in increased number of circulating EPCs, improved neurobehavioral outcomes, and significantly reduced the incidence of recurrent stroke at 90 days [67]. EPO induces VEGF production and improves the survival and proliferation of EPCs via the PI3K/Akt pathway [68]. Experimental and clinical studies in patients with ischemic stroke have demonstrated that the administration of statins increases the number of circulating EPCs and improves their angiogenic and vasculogenic functions [69]. The underlying molecular mechanisms might be related to the production of NO, a key inducer of EPCs in vascular repair [69]. Granulocyte-colony-stimulating factor (G-CSF) increase multifunctional VEGF levels and the expression of CXCR4, a homing receptor; these facilitate the migration of EPCs from the BM into the peripheral circulation and their recruitment to the sites where repair of the endothelium is required [70]. VCAM-1 is expressed on BM stromal cells and participates in retaining progenitor cells with the BM. G-CSF degrades VCAM-1 through the release of elastase and cathepsin G upon activation of neutrophils in the BM, leading to EPC mobilization [33]. SDF-1 appears to be a critical positive factor that is associated closely with the cellular functions of EPCs [71]. Increasing evidence has revealed that SDF-1 plays an essential role in recruiting circulating EPCs into ischemic regions and the regeneration of injured tissue after cerebral ischemia [38]. Serum SDF-1 levels increase significantly following acute ischemic stroke, and these changes are positively correlated with infarct volume and stroke severity [72]. High levels of SDF-1 are detected in the cortical peri-infarct regions, which are relevant to promoting positive outcomes of the disease [56, 73]. Application of AD300, a special antagonist to CXCR4, significantly reduces the number of EPCs and capillary density in ischemic tissues after middle cerebral artery occlusion (MCAO) [74]. SDF-1 interacts with CXCR4, a receptor expressed on the surface of EPC, to regulate the movement of EPCs from the BM into the peripheral circulation and their subsequent movement into areas of ischemic injury. Hyperglycemia and hypertension, common risk factors for ischemic stroke, are associated with dysfunction of vascular remodeling, impaired neovascularization, and impaired EPC functions, which can be reversed by treatment with SDF-1 [75]. Recently studies have indicated that decreased levels of CXCR7 expressed on EPCs are associated with progenitor cell dysfunction in diabetic or hypertensive conditions [75]. Further studies have demonstrated that SDF-1/CXCR7 is a survival signal associated with cellular defense against oxidative stress and cell survival under various pathological conditions [40]. These studies demonstrate that SDF-1 might be a therapeutic target to improve the functions of EPC in the repair of cerebral injury after ischemic stroke.

Conclusion

In conclusion, EPCs are endothelial precursor cells capable of proliferating and differentiating into mature ECs. These progenitor cells contribute to the recovery and reconstruction of injured cerebral tissue by promoting neovascularization and secretory mechanisms and could provide novel potential therapies for ischemic stroke. The therapeutic efficacy of EPCs is closely related to their number and functional activities. Pharmacological agents have been shown to increase the recruitment and retention of EPCs in ischemic regions and promote revascularization and restoration of blood supply in injured tissues. SDF-1 plays a critical role in mobilizing EPCs from the BM to enter into the peripheral circulation and then recruits the circulating EPCs to locate into the ischemic tissues. Thus, SDF-1 appears to be a potential target for improving EPC function in vascular repair and regeneration. The development of new strategies to increase local levels of SDF-1 could increase the therapeutic efficacy of EPCs in treating ischemic disorders. Therefore, further elucidation of such strategies is needed.

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Declarations

Ethical approval None.

Competing interests The authors declare no competing interests.

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