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The mechanisms and applications of endothelial progenitor cell therapy in the treatment of intracranial aneurysm

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Abstract

The pathophysiological mechanism of intracranial aneurysm (IA) involves the dynamic interaction of ECM abnormalities, hemodynamic stress, and inflammatory response. The rupture of intracranial aneurysm will cause serious consequences. Multiple studies have confirmed the important role and potential application of endothelial progenitor cells (EPCs) in vascular repair. This review focuses on the specific mechanism of EPCs in the treatment of intracranial aneurysms, which promote re-endothelialization and angiogenesis through bone marrow mobilization, targeted migration to the site of injury, differentiation into mature endothelial cells, and secretion of angiogenic factors. In addition, EPCs maintain ECM homeostasis by regulating MMP/IMP balance, inhibiting aneurysm wall thinning and structural damage. Based on the vascular repair mechanism of EPCs, new treatment strategies such as "biologically active" spring coils (loaded with EPCs or SDF-1α) and flow diverters(FDs) combined with EPCs therapy have been developed to synergistically promote carotid endothelialization of aneurysms and reduce the risk of recurrence. Future research needs to further validate the long-term efficacy and precise regulatory mechanisms of EPCs in clinical translation, providing new directions for IA treatment.

Keywords Intracranial aneurysm, Endothelial progenitor cell, Endothelialization, Endovascular treatment

Background

Intracranial aneurysms(IAs), refer to a localized dilation of the arterial walls within the brain. This abnormality most often occurs at branching points in the circle of Willis [1–3]. Epidemiological studies suggest that the prevalence of IAs falls between 0.5% and 3% of the general population [2, 4]. When these aneurysms rupture, they can lead to a wide array of severe and life-threatening clinical complications. These may include subarachnoid hemorrhage (SAH), compression of adjacent brain tissue, dysfunction of cranial nerves, hemiparesis, visual disturbances such as defects in the visual field, seizures, pressure on the brainstem, transient ischemic attacks, and in some cases, cerebral infarction due to distal embolization. These conditions can significantly impair

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neurological function and are associated with a high risk of mortality [2].

The exact origins of IAs are not yet fully elucidated. While genetic factors are suspected to play a significant role in some individuals, other cases may be influenced by external triggers such as infections or inflammatory responses. The development of IAs involves a multifactorial process where genetic predisposition, mechanical forces from blood flow, and abnormalities in the arterial walls collectively contribute to the condition. Several known risk factors, including chronic hypertension, tobacco use, and mutations in specific genes, can lead to the weakening and thinning of the arterial walls, providing the necessary conditions for aneurysm formation and, in some cases, rupture [5–8]. In addition, the abnormal functioning of certain vascular cells, such as endothelial progenitor cells (EPCs) and vascular smooth muscle cells (VSMCs), which are essential for maintaining and remodeling the vascular wall, has been suggested to play an important role in the pathogenesis of IAs [9, 10].

EPCs are a subtype of cells that originate from $CD34^+$ hematopoietic stem cells in adults. These cells have the remarkable ability to differentiate into endothelial cells when cultured in vitro, which makes them an essential component in vascular repair and regeneration [11]. EPCs contribute significantly to maintaining vascular health by stabilizing the endothelial layer and replenishing damaged endothelial cells, thus ensuring the proper function of blood vessels [12, 13]. EPCs are integral to maintaining the overall health of the vasculature, supporting the repair of damaged vessels and fostering the formation of new blood vessels. Furthermore, these cells have been proposed as biomarkers for assessing cardiovascular disease risk, given their involvement in vascular repair and regeneration [14, 15]. However, under certain conditions such as aging, smoking, hypertension, and IAs, the number of circulating EPCs has been shown to decline significantly [16].

Numerous studies investigating EPCs have unveiled significant therapeutic targets and novel approaches for the treatment and management of cardiovascular diseases. Similarly, gaining a deeper understanding of the roles EPCs play in cerebrovascular conditions is essential for overcoming the challenges in treating IAs and related disorders. It is believed that a disruption in the homeostatic balance between the vascular endothelium and its repair mechanisms increases the vulnerability of the vascular wall to hemodynamic stress, which can ultimately contribute to the formation of IAs [12, 17]. In individuals with IAs, endothelial cells are the first to be affected following vascular injury, and a noticeable decrease in endothelial cell numbers is observed in IAs [18]. The alterations in both the quantity and function of circulating EPCs suggest that these cells are crucial in the pathogenesis of IAs and its progression [19]. Investigations into the role of endothelial repair in IAs development have led to the following conclusions: (1) A decrease in EPC levels is linked to the development of IAs; (2) EPCs are recruited to the aneurysm wall, where they play a significant role in repairing and remodeling the aneurysm; and (3) EPCs promote endothelialization after interventions such as coiling embolization and the implantation of flow diverter (FD) stents [20–23].

EPCs serve as a fundamental initiating factor in the re-endothelialization process that follows endovascular treatments aimed at occluding aneurysms [24, 25]. Various targeted interventions that aim to enhance the mobilization of EPCs and increase their presence in the bloodstream have shown promising results in preclinical models of IAs [24]. Recent findings show EPCs hold significant promise as a part of therapeutic treatments for IAs. EPCs are recognized as pivotal factors in the endothelialization process that follows blood flow diversion. The neointimal tissue begins to grow along the surface of the device, progressively extending and eventually forming a barrier that isolates the aneurysm from the arteries that supply it [26]. This endothelial coverage, which forms over time, is essential for achieving sustained occlusion of the aneurysm, as it ensures the long-term sealing and isolation of the lesion from the surrounding blood vessels [27].

At present, a variety of treatment options are available for managing IAs. The choice of treatment is determined by assessing several factors, such as the aneurysm size, shape, location, and the condition of its wall, all of which contribute to evaluating the rupture risk. Based on this evaluation, the most suitable treatment approach is selected. In general, the therapeutic strategies include surgical clipping, interventional treatments, and conservative management. The choice of interventional method is often based on the aneurysm's specific characteristics, such as its shape and size, which influence the selection of materials and techniques. Options for interventional treatment include simple coil embolization, stent-assisted coil embolization, flow-diverting stents, and devices designed to disrupt the aneurysm internally, such as intratumoral spoilers [28–30].

The investigation into interactions between EPCs and IAs at pathological stages will help clarify how these conditions develop along with their progressions providing an advanced foundation for creating effective new treatment methods. This review examines EPC functions in IAs management then evaluates EPCs as therapeutic targets to prevent and treat IAs.

Biological characteristics of EPCs

Endothelial precursor cells known as EPCs functionally serve vascular regeneration because they reside mainly within the specialized domains of bone marrow stem cell niches [11]. The presence of EPCs extends beyond their primary bone marrow locale to umbilical cord blood as well as peripheral circulation and arterial walls but detectives discover their quantities diminish in these further locations [31–33]. The EPC population shows great heterogeneity because it contains cells at multiple endothelial differentiation phases accompanied by distinctive phenotypic traits and functional abilities. Research has established a characteristic profile for this population using surface markers CD34, CD133, CD31, VEGFR-2, vWF, CD144, Tie2, CD117, CD62E, and CD45 which serve as standard definitions for EPCs [34–38]. EPCs that exhibit $CD133^+$, $CD34^+$, and $VEGFR\text{-}2^+$ marker expression represent less mature developmental stages of these cells as identified in reference [35]. The maturation of EPCs results in a progressive decline of specific surface markers including $CD133^+$. These markers are no longer present in mature endothelial cells (ECs), highlighting the dynamic process through which EPCs differentiate into fully functional endothelial cells [39]. Endothelial progenitor cells (EPCs) can be isolated from diverse sources such as bone marrow, peripheral blood, umbilical cord blood, and adipose tissue. Importantly, EPCs from different origins exhibit distinct functional and phenotypic characteristics, which may significantly impact their therapeutic efficacy: Bone marrow-derived EPCs are enriched in CD34+/VEGFR-2 + populations and demonstrate strong migratory capacity toward ischemic tissues, making them ideal for ischemic vascular repair [40]. Peripheral blood-derived EPCs are mobilized in response to hypoxia or cytokines (e.g., SDF-1α) but show lower proliferative potential compared to BM-EPCs [41]. Umbilical cord blood-derived EPCs exhibit higher clonogenic activity and enhanced paracrine secretion of angiogenic factors (e.g., VEGF, Ang-1), suggesting advantages in neovascularization therapies. These source-dependent variations necessitate careful selection of EPCs tailored to specific clinical applications [42].

EPCs are a distinct group of precursor cells that are involved in endothelial cell regeneration and repair. They can be classified into two categories based on their time in culture: early EPCs (eEPCs) and late EPCs (lEPCs) [43]. This classification reflects the different stages of maturation that these cells undergo. eEPCs typically appear within the first 4 to 7 days of culture, whereas lEPCs generally emerge after 14 to 21 days of culturing [44]. eEPCs share phenotypic and functional similarities with $CD14^+$ cells and are often referred to as $CD14^+$ EPCs. Escleman et al. described these cells as originating from the bone marrow or hematopoietic progenitor cells, with a distinct spindle-shaped morphology [45]. The markers typically associated with eEPCs include CD31, CD133, CD34, VEGFR-2, vWF, CD45 (a hematopoietic-specific antigen), and markers like CD14 and CD115, which are characteristic of monocytes and macrophages [35, 46, 47]. These cells are capable of taking up acetylated low-density lipoprotein and binding to the lectin Ulex europeus agglutinin-1 (UEA-1), which are functional traits commonly attributed to mature endothelial cells (ECs) [48]. The combination of these surface markers illustrates their dual functionality, as they exhibit properties of both endothelial and hematopoietic cells. This dual characteristic suggests that eEPCs may contribute to processes such as vascular repair and may also play a role in inflammation.

Late endothelial progenitor cells (lEPCs), sometimes referred to as outgrowth endothelial cells or $CD34^+$ EPCs, are closely related to the circulating $CD34^+$ hematopoietic stem cells that originate in the bone marrow [49]. Cellular cobblestone-like morphology serves as the primary visual distinction between these cells and eEPCs according to reference [50]. lEPCs lack monocyte and macrophage-associated surface markers CD14 and CD115 whereas eEPCs express these markers [51]. Markers CD34 and CD133 along with VEGFR-2 which EPCs express remain inadequate for identification since other cell types share these same markers [52, 53](Fig. 1). The cytokine levels in eEPCs and lEPCs show major differences between the two types. According to research findings from Yoon et al. that eEPCs showed positive expression for CD14 and CD45 markers but lEPCs did not carry the same markers [38]. The research discovered that lEPCs demonstrate higher KDR and chemokine receptor 1(CXCR-1) levels relative to eEPCs. Examination of the cell markers VE-cadherin along with Fms-related receptor tyrosine kinase (Flt-1), KDR and CD45 reveals different expression profiles between these subpopulations. The secretion of angiogenesis-regulating cytokines like VEGF and IL-8 is stronger in eEPCs than in lEPCs when studied in lab cultures yet both EPCs show equal angiogenesis promotion capabilities during live testing [35]. Moreover, surface markers linked to hematopoiesis, such as WAS and LYN, are expressed at significantly lower levels in lEPCs than in eEPCs [54]. In addition, studies by Zhang et al. have shown that eEPCs exhibit limited proliferative potential and are nearly incapable of being passaged, whereas lEPCs demonstrate significantly higher proliferative capacity and the ability to form capillary-like structures, resembling the behavior of microvascular endothelial cells [55].

However, in terms of the EPCs endovascular treatment of IAs, the cell surface markers of EPCs might play a more important role in the capture, homing, proliferation and differentiation despite the type or origin. One

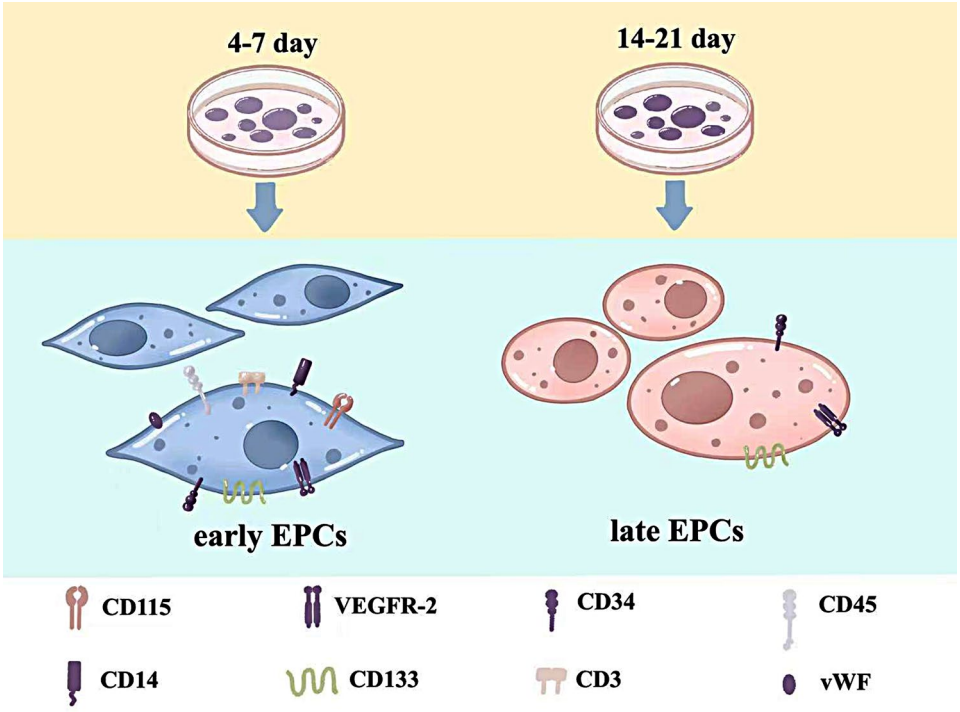

Fig. 1 Two different types of EPC. Early EPCs Originating from bone marrow or hematopoietic progenitor cells, spindle shaped. Cultivation period: 4–7 days. Markers: $CD14^{+}/CD115^{+}$ (monocyte/macrophage characteristics), $CD31/CD34/CD133/VEGFR\text{-}2/CD45^{+}$ (dual markers of endothelium and hematopoiesis). Function: Intake of Acetylated low-density lipoprotein and binding to UEA-1; Secreted high levels of VEGF/IL-8; Promotes angiogenesis but weak proliferative ability, making it difficult to propagate. Potential role: vascular repair and inflammation regulation. Late EPCs Source and morphology: Derived from bone marrow $CD34^{+}$ hematopoietic stem cells, with a pebble like morphology. Cultivation period: 14–21 days. Markers: $CD14^{-}/CD115^{-}$, high expression of KDR/CXCR-1; Low hematopoietic related markers (WAS/LYN). Function: Strong proliferative ability, capable of forming capillary like structures; The in vitro angiogenic activity is comparable to eEPC. Characteristics: It is closer to mature endothelial cells and exhibits microvascular endothelial behavior

clinical trial in 2005 showed that G-CSF administered to patients increased $CD133^{+}/VEGFR\text{-}2^{+}$ EPCs and endothelial cell-forming clusters in culture [56]. Similarly, it had been demonstrated that one subpopulation of EPCs of $CD34^{-}/CD133^{+}$ not only significantly showed higher rates of proliferation ($P < 0.005$), but also a higher potential of celldifferentiation capacity into other cell types which might be applied to the more capture in situ of EPCs through grafting CD133 antibody to surface coating of blood-contact materials [57, 58].

Mechanisms of EPC in the treatment of IAs

The pathophysiology underlying IA is multifactorial, encompassing three main interconnected mechanisms: abnormalities in the ECM, hemodynamic stress, and inflammatory responses. These factors are not only interconnected but also influence each other in a dynamic and complex manner. The ECM plays a crucial role in preserving the mechanical strength and elasticity of the vessel wall. When defects or alterations occur within the ECM, the structural integrity of the vessel is compromised, which can facilitate the formation of aneurysms. One of the key contributing factors to aneurysm formation is increased wall shear stress, which induces endothelial cell injury, smooth muscle cell degradation, and thinning of the vascular media. Changes in blood flow patterns are central to the pathogenesis of aneurysm formation because they influence the localization of inflammatory cells and regulate endothelial cell responses to localized inflammation. Hemodynamic alterations lead to the recruitment of inflammatory cells and the release of pro-inflammatory cytokines, which in turn amplify the local inflammatory environment and perpetuate damage. The endothelial lining, as the primary sensor of changes in shear stress, plays an essential role in modulating inflammatory processes. An intact and functional endothelial monolayer contributes to vascular homeostasis by secreting anti-thrombotic and anti-inflammatory mediators, thus helping protect the vessel wall from excessive inflammation and thrombus formation [59–62]. The formation of aneurysms is widely believed to be the result of an imbalance between factors that promote endothelial injury and those that initiate repair processes [63, 64]. Injury to endothelial cells sets off an inflammatory cascade in the vessel wall, leading to the accumulation of inflammatory cells and the secretion of cytokines, both

of which exacerbate the damage to the vessel wall. This inflammatory response also triggers the phenotypic transition of VSMCs, further contributing to aneurysm formation. Key components of the inflammatory process, such as adhesion molecules, cytokines, ROS, leukocytes, MMPs, and VSMCs, are central to the progression of this pathological state [65, 66]. Among these, monocytes, particularly macrophages, play a critical role in driving the inflammatory cascade. Macrophages release MMP-2 and MMP-9, enzymes that are involved in the breakdown of ECM components and the remodeling of the vascular wall. These enzymes are instrumental in both the formation and rupture of aneurysms, as they degrade the ECM, weaken the vessel wall, and promote structural changes that facilitate aneurysm progression [17, 67].

EPC promotes vascular endothelial repair and vascular wall stability

The vascular endothelium serves as the first line of defense in shielding the vascular walls from the stresses induced by chemical agents, inflammation, and mechanical forces [60]. The body possesses an innate repair system for addressing endothelial damage or dysfunction, which involves the activation of multiple signaling pathways and the recruitment of various repair cells [68]. Research has shown that EPCs play a crucial role in maintaining the integrity and function of the vascular environment by promoting processes such as neovascularization and the re-endothelialization of injured blood vessels [69]. Under normal, healthy conditions, EPCs are primarily located in the bone marrow (BM) microenvironment, which is characterized by low oxygen levels and a high concentration of stromal cell-derived factor-1 alpha (SDF-1α), while their presence in circulating blood is minimal [70]. However, when inflammation, injury, or hypoxia occur, EPCs are "mobilized" from the BM and enter the bloodstream in response to trigger factors such as chemokines, MMP-9, VEGF, and NO produced by damaged blood vessels [71, 72]. The primary factor that initiates the mobilization of EPCs from the BM to the sites of injury in peripheral blood is the release of angiogenic growth factors during ischemic damage, which includes granulocyte-forming factors, GM-CSF, VEGF, and SDF−1α [73, 74]. In response to injury, damaged tissues and platelets release cytokine SDF-1α, which binds to the CXCR-4 receptor on the surface of EPCs, leading to the activation of MMP-9 in combination with growth factors [75]. This interaction also results in the release of SKITL that binds to c-kit, ultimately creating a proliferative BM microenvironment that supports EPC migration [76, 77]. SDF-1α demonstrates additional mobilizing capability by interacting with factors G-CSF and VEGF as well as E-selectin and activating eNOS-dependent signal transduction pathways to drive CXCR4 + stem and progenitor cells from the body into blood circulation [78]. Studies demonstrated that SDF-1 administration leads to elevated VEGF production within ischemic areas and thus raises circulating EPC levels [79]. Research shows infection produces higher plasma amounts of IFN-γ together with VEGF, G-CSF and SDF-1 while also enhancing signal transmission between Sca-1 and RAS-related C3 botulinum toxin substrate 2 (Rac2) within bone marrow-derived EPCs which results in boosted EPCs expression [80].

SDF-1α plays a significant role in regulating the expression of PSGL-1 on progenitor cells [75]. Research has demonstrated that the levels of PSGL-1 expression following vascular injury are dependent on the concentration of SDF-1α, which modulates the response in a dose-dependent manner. PSGL-1 is a ligand for P-selectin, a molecule found on aggregated platelets in damaged blood vessels [81–83]. When endothelial damage occurs, platelet activation leads to the release of P-selectin, which in turn binds to PSGL-1 on EPCs, promoting their aggregation at the injury site. In addition, CD34, a surface marker on EPCs, acts as a ligand for E-selectin. The interaction between E-selectin and CD34 enhances the adhesion of EPCs to the ischemic endothelium. Furthermore, SDF-1α amplifies the migration and repair functions of EPCs by stimulating the expression of E-selectin, thereby fostering EPC recruitment to areas of endothelial damage [84]. Based on this, the above research proved the application potential of SDF-1α in vascular wall repair. Studies that applied SDF-1α-together-coated coils established that autologous mesenchymal stem cells administration provided structural strengthening of the aneurysm sac while decreasing its volume [21].

EPCs play a pivotal role in vascular repair by adhering to sites of tissue injury through integrins. Upon attachment, EPCs contribute to neovascularization and re-endothelialization by transforming into mature ECs and remodeling the extracellular matrix components of the damaged tissue [85, 86]. The paracrine signals derived from EPCs play a key role in creating an angiogenesis-promoting microenvironment that supports both the formation of new blood vessels and the regeneration of the existing vasculature. Upon mobilization, EPCs further attract various angiogenic growth factors such as G-CSF, GM-CSF, HGF, and VEGF [48]. These growth factors activate various intracellular signaling pathways, including those involving phosphatidylinositol 3-kinase(PI3K) and mitogen-activated protein kinase(MAPK) [87]. The downstream effects of these pathways contribute to the creation of a microenvironment that facilitates endothelial cell proliferation and supports tissue repair in the affected area.

EPCs are crucial in maintaining endothelial integrity by producing angiogenic factors that promote the

proliferation, survival, and functionality of mature ECs, as well as other neighboring progenitor cells, such as smooth muscle progenitor cells and other vascular progenitors [88]. EPCs also possess the ability to migrate toward areas of injury, where they differentiate into functional endothelial cells, restore the integrity of the endothelial barrier, enhance the stability of the vascular wall, and decrease the likelihood of aneurysm rupture by upregulating the expression of VEGF, SDF-1α, and CXCR4 [89]. Through modulation of MMP-2 and MMP-9 levels against their TIMP inhibitors, EPCs prevent structural tissue damage to elastin and collagen sustaining vascular wall durability. According to studies conducted on rodents the injection of EPCs demonstrates both the reduction of aneurysm wall thinning along with the maintenance of the inner elastic layer and promotion of new extracellular matrix deposition within the vessel wall [90].

In view of the problem that the endothelial coverage rate of intracranial aneurysms after traditional coil embolization is less than 50% and easy to relapse, "bioactive" coils have been developed to improve the long-term stability of the procedure, ongoing research remains dedicated to enhancing the rate of endothelialization at the aneurysmal neck. At 16 weeks post-treatment patients treated with EPCs developed uniform endothelial cell layers along with beneath neointima formations across their aneurysm neck [20]. The current research reveals that EPCs show targeted movement toward coil curls leading to endothelial cell expansion which supports the entire endothelialization mechanism [24]. Different microRNAs have become the focus of additional research for potential impacts on endothelialization rates after coil embolization. Yu et al. discovered that mir-31a-5p microRNA generates enhanced circulation and functional ability for EPCs to migrate and make new endothelial layers [91].

Flow diverter and EPCs synergistically promote endothelialization. Immediately after the flow diversion treatment, the first observable event is the adhesion of clusters of inflammatory cells to the neck of the aneurysm, injury to the vessel's endothelial layer triggers a cascade of responses, leading to the release of several cytokines, including VEGF, FGF, SDF-1α, NO, CXCR-8, and Angiopoietin-1 [92]. These signaling molecules contribute to the activation and proliferation of local endothelial cells as well as SMCs, which play essential roles in the healing process of the injured tissue [93]. Additionally, these cytokines promote the migration of EPCs toward the site of vascular damage [94](Fig. 2).

Angiopoietin-1 is an important pro-angiogenic factor, known for its pivotal function in stimulating vascular remodeling. It achieves this by interacting with the Tie-2 receptor, which is expressed on the surface of endothelial cells [95]. The role of this signaling pathway becomes particularly crucial within the bone marrow, where it helps to maintain hematopoietic stem cells in an undifferentiated state. After ischemic injury, the expression of Angiopoietin-1 increases significantly in brain endothelial cells, suggesting its vital involvement in vascular repair mechanisms [96, 97].

Endothelialization, a process that takes time, is primarily driven by endothelial cells originating from the adjacent parent artery, making it a gradual event [22]. Simultaneously, the structural elements of the FD itself, namely the struts, act as a supportive scaffold, aiding the migration of endothelial cells from both the proximal and distal sections of the parent artery [98]. Endothelialization occurs in two distinct phases: the first is a rapid, early phase characterized by the widespread migration of cells from the surrounding tissue, followed by a slower, later phase where the device's structure plays a supportive role. During this latter phase, EPCs migrate to the injury site, aided by the scaffolding provided by the stent. EPCs originating from the bone marrow are essential for the neointima formation and re-endothelialization processes that occur after the aneurysm is treated with elastase-induced blood flow diversion. These EPCs can differentiate into various cell types depending on the progression of neointima formation, demonstrating their plasticity and adaptability in response to the tissue environment [99]. In preclinical animal models, the process of endothelialization following the implantation of a FD typically spans a period of 4 to 8 weeks. However, early changes can be observed as soon as the first day after the deployment of the stent, with the appearance of patchy distributions of $CD31^+$ endothelial cells along the metal struts of the device [22]. This initial response is a critical part of the vascular healing process. Further research into endothelialization in blood flow guidance devices has been conducted using rabbit aneurysm models, where the migration and behavior of EPCs have been closely observed. Utilizing immunolabeled scanning electron microscopy with $CD34^+$ markers, it was found that by the 60th day after implantation, up to 87–90% of the surface area of the device was covered by new tissue growth [100].The mechanisms of EPCs in the treatment of intracranial aneurysms are showed in the Fig. 2.

Based on the basic idea of promoting EPCs migration and strengthening endothelialization, many studies have been carried out on FD stent coating. Modern coating advances for FD stents aim to reduce thrombotic risk while actively driving neointimal growth that stabilizes long-term vessel repair. The current biomedical research focuses on developing new stents covered with biofactors that produce two biological actions which serve anticoagulation and endothelialization. The field of cerebrovascular interventions has gained a promising new treatment strategy which uses stents covered with

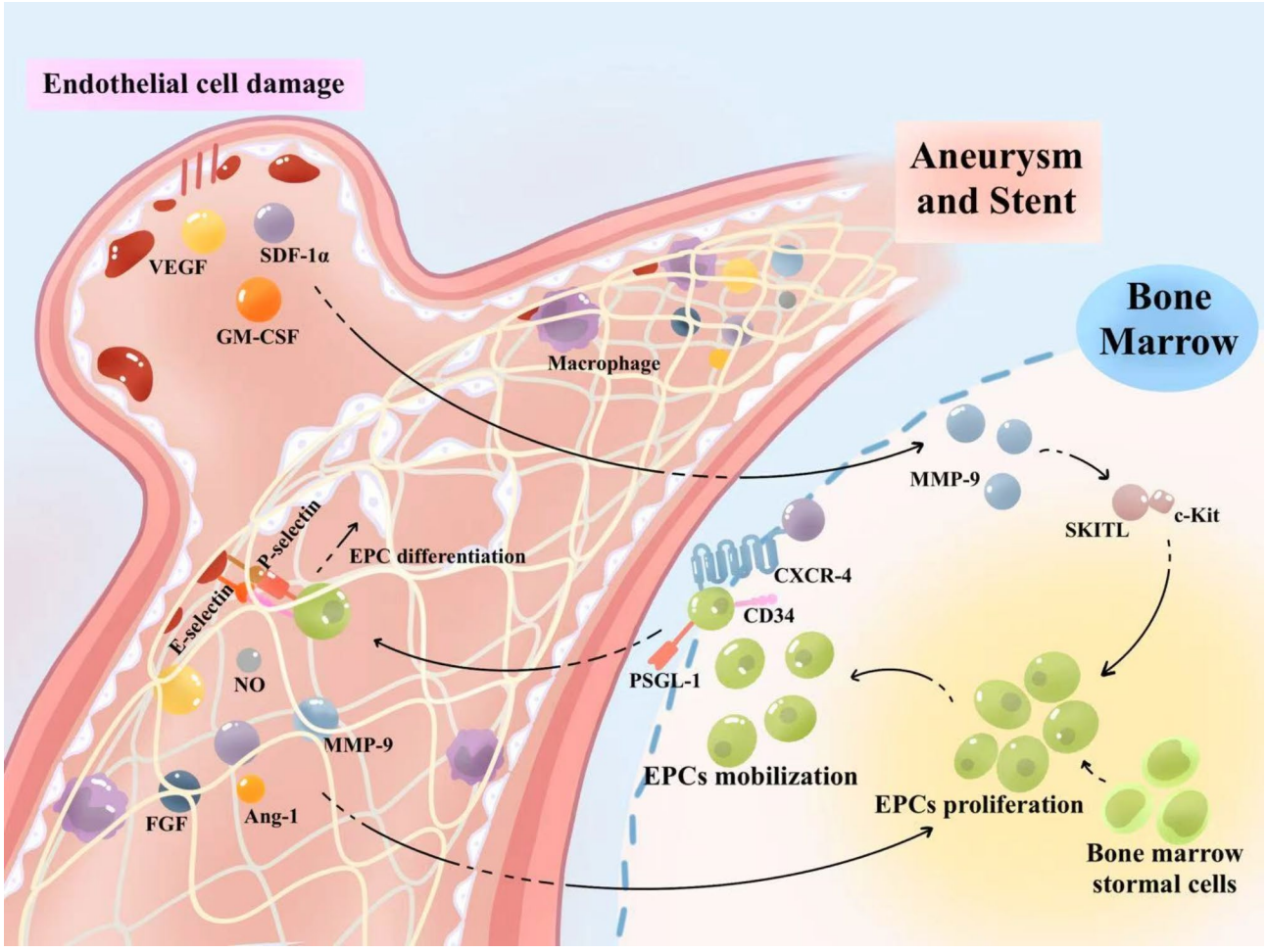

Fig. 2 Flow diverter and EPCs synergistically promote endothelialization. After stent implantation, inflammation of the vascular wall is triggered firstly, attracting inflammatory cells and a series of inflammatory factors are released including VEGF, FGF, SDF-1α, NO, CXCR-8, and Angiopoietin-1 these cytokines promote the proliferation and migration of EPCs toward the site of vascular damage. After the mobilization, the surface markers PSGL-1 and CD34 are combined with P-selectin and E-selectin accordingly. Then the EPC differentiate into endothelial cells along the scaffold, and a new endothelial layer is formed eventually. The damaged endothelial cells also release some cytokines like VEGF, SDF-1α, GM-CSF, which can activate MMP-9, then trigger the combination of SKITL and c-Kit that enhance the proliferation and mobilization of EPCs

anti-CD34 antibodies. The current treatment emerged from previous findings which showed these coatings enhance EPC migration to damaged vascular sites and improve recovery for patients with aneurysms and vascular problems [101]. FD stents now benefit from a significant development through the application of CD31 surface coatings. The transmembrane glycoprotein CD31 recognized as PECAM-1 facilitates both adhesion and movement within endothelial cells. Clinical studies verify that FD stents perform better when CD31 coatings help them bond with the vascular wall because of the importance of device integration for treatment success. When applied the coating becomes dual-purpose by increasing both endothelial cell adhesion to the surface and reducing inflammatory responses that create favorable conditions for healing. The histological examination of the arterial wall created using CD31-coated FD stents at the aneurysm neck shows evidence of neovascularization structure development. The newly formed endothelial structure appears like arterial middle layers through its distinct thick collagen composition positioned adjacent to a strong smooth muscle cell arrangement [102].

Dual-action stents aim to better aneurysm treatment outcomes by delivering improved occlusion while reducing the complication risks of endovascular interventions. Construction of biofactor-coated scaffolds has been accomplished with nickel-titanium alloy sheets. The scaffold sheets contain both VEGF and anti-CD34 antibodies which induce endothelial cell growth while supporting EPC recognition and adhesion. Scientists have proven that nickel-titanium alloy sheets support bioactive scaffolds to carry VEGF and anti-CD34 antibodies which function as principal drivers of the healing mechanism. The experimental results demonstrate these scaffolds

possess superior blood compatibility in research tests. Though these materials support both the growth of human umbilical vein endothelial cells (HUVECs) they help to bind the EPCs effectively. These results reveal biofactor-coated scaffolds show promise as essential tools for better aneurysm intervention results and safe endovascular practice which promises substantial clinical application opportunities [103]. In the year 2021 Pipeline Flex Embolization Device (PED) shield technology within the Pipeline Flex system secured FDA marketing approval as the third-generation blood flow guidance device. The first design purpose of this device focused on thrombosis reduction through choline phosphate coating. Scientific investigations show that PED shield enhances early endothelial cell development during pig aneurysm procedure testing into practice [104]. Clinical evaluations of the PED shield revealed safe performance data because it achieved occlusion rates between 81% and 92% throughout a one-year period according to studies [105–107].

Recent advancements in bioengineering have increasingly focused on developing biodegradable scaffolds with integrated cell-therapeutic functions hat hold regenerative potential for vascular applications. A variety of biodegradable scaffold designs are being explored as promising options for the treatment of IA, particularly when combined with EPC delivery to address both structural and biological repair. Among the most commonly utilized materials for biodegradable scaffolds are PLA and PLGA, both of which offer significant advantages in terms of biocompatibility and controlled degradation [92]. Upon implantation of a blood flow-guided stent, the release of cytokines stimulates endothelial and smooth muscle cell activity, which in turn promotes the mobilization of EPCs to the site of vascular injury. Moreover, scaffolds that are coated with antibodies capable of capturing EPCs and facilitating endothelialization present an exciting potential therapeutic approach in the future [92]. Emerging strategies such as 3D-bioprinted hybrid scaffolds pre-seeded with EPCs demonstrate a promising treatment for enhancing bone defect repair which is hopeful for the treatment of IAs [108].And hydrogel surfaces have been improved to enhance the attachment and adhesion of EPCs [109].

Nishi and colleagues were pioneers in developing the first fully bioabsorbable FD made from 48 braided poly-L-lactic acid fibers [110]. Further investigation by Jamshidi et al. using PLA revealed that in some cases, stent vessel wall non-adherence led to local thrombosis, raising concerns about the safety of these materials [111].

During vascular healing processes, EPCs provide essential endothelial cell support so that through their angiogenic factor secretion including VEGF and FGF and the cytokine IL-10, they promote proper vessel regeneration. New blood vessel development alongside existing vasculature regeneration results from these environmental support constructs. EPCs help generate a protective endothelial layer at treated aneurysm sites that prevents platelet aggregation while reducing thrombosis rates resulting in decreased recurrences. NO and PGI2, both secreted by EPCs, play a key role in providing antithrombotic protection by inhibiting platelet activation and aggregation [112, 113]. Thrombosis often complicates interventional treatments, particularly after embolization and blood flow diversion procedures, contributing to treatment failure. EPCs can mitigate this risk by contributing to the formation of a complete endothelial layer in the aneurysm neck, which decreases platelet adhesion and, as a result, reduces the risk of clot formation. Furthermore, EPCs are instrumental in the repair of vascular endothelium, restoring smooth vascular surfaces, reducing the occurrence of thrombosis in areas of endothelial injury, and minimizing complications that can arise after interventional procedures [114, 115]. It has been demonstrated that the CD146 Ab-armed nanofilamentous stent could show great performance in the reduction of thrombosis and restenosis through re-endothelialization due to highly efficient late EPCs cell capture [116].In a clinical trial which aimed to evaluate whether quantitation of peripheral blood endothelial progenitor cells (EPCs) could improve prediction of unprovoked venous thrombosis(VTE) recurrence risk showed that levels of EPCs were lower in patients who developed VTE recurrence [117].

In individuals suffering from IA, the concentration of EPCs in circulation is typically reduced. In addition, their migration, adhesion, and senescence capabilities are often enhanced, which may contribute to disease progression [19, 118]. Numerous studies have utilized various clinical pharmacological agents to stimulate the mobilization of EPCs and direct their recruitment to sites of aneurysm formation. For instance, preclinical animal models have shown that statins, including rosuvastatin and atorvastatin, effectively promote the movement of EPCs from the bone marrow. This enhanced EPC mobilization facilitates endothelialization at the aneurysm neck, which helps reduce aneurysm degeneration and contributes to overall vascular healing [119, 120]. Further research has demonstrated that autologous blood transfusions involving EPCs result in these cells preferentially migrating to the neointima of damaged blood vessels [121]. Additionally, elevated erythropoietin levels have been shown to stimulate the migration of EPCs to injured areas [16], while sitagliptin has been found to support vascular repair by enhancing EPC migration and aiding the healing process of damaged vasculature [122].

Regulate local inflammatory response

An increased local inflammatory reaction along with oxidative stress occurs during aneurysm development. Macrophages and T cells move into injured blood vessels while secreting inflammatory substances including TNF-α and IL-1β together with MMPs. The production of ROS undergoes simultaneous elevation. The combined factors lead to significant vascular wall deterioration and enlarged aneurysm expansion over time [123]. EPCs control inflammatory progression by blocking macrophage activation together with their migratory activity. The reduction of pro-inflammatory factors achieves the slowing of local inflammation while simultaneously promoting vascular stabilization. Endothelial Progenitor Cells release anti-inflammatory cytokines like IL-10 and TIMP-1 to control local immune response and reduce inflammation-related vascular damage after vessel wall rupture events [124, 125]. Research identified that EPCs block MMP activity, including that of MMP-2 and MMP-9 which results in decreased degradation of the aneurysm wall matrix. Such treatment causes aneurysm walls to heal and slows down both their outward growth and deteriorating progression. EPC intervention creates favorable conditions that allow therapeutic approaches to function more effectively in retreating aneurysms [90]. New studies demonstrate how exosomes produced by EPCs demonstrate promising therapeutic potential. According to Ma et al.'s study endothelial cells generate dangerous levels of ROS after hypoxia/reoxygenation(H/R) trauma leading to vascular malfunction. Under H/R injury endothelial cells undergo increased apoptosis which EPC-derived extracellular vesicles help to reduce by also protecting against excessive ROS production thereby demonstrating EPC potential for vascular regenerative therapy [125].

The treatment of IAs through interventional methods is frequently combined with drug therapies to enhance the process of endothelialization at the aneurysmal neck. Among these drugs, aspirin is widely acknowledged for its antiplatelet and anti-inflammatory effects. It has been demonstrated in animal models, particularly rats, to notably reduce degeneration of the aneurysmal wall. This protective effect is attributed to the increased mobilization of EPCs and a reduction in chronic vascular inflammation mediated by macrophages [126]. In the same aneurysmal tissues, RT-PCR analysis has shown a reduction in the expression of various inflammatory markers, including NF-κB, MCP-1, and VCAM-1, in mice treated with cilostazol when compared to those in the control group [127]. Additionally, a recent study by Suzuki et al. [128] reinforced the beneficial impact of Cilostazol on the rupture rates of induced IAs in mice. While the formation rate of aneurysms between the Cilostazol-treated group and the control group did not present significant statistical differences, a noteworthy reduction in the rupture rate was observed in the Cilostazol group. In addition to these findings, statins and aspirin have been shown to not only promote the proliferation of EPCs but also inhibit inflammatory responses in the aneurysmal wall. These pharmacological agents reduce the expression of several key inflammatory factors, including iNOS, MMP-2, MMP-9, VEGF, NF-κB, and MCP-1. Previous studies have highlighted the role of sustained hemodynamic shear stress, which leads to endothelial dysfunction at vascular bifurcations, triggering inflammatory responses. This inflammatory activation is followed by the invasion of immune cells such as macrophages, T lymphocytes, and B lymphocytes into the aneurysmal tissue, which leads to further damage of the vascular wall [12, 129]. Therefore, these dual-action drugs, which stimulate EPC mobilization while simultaneously reducing inflammation, may be more effective in stabilizing the aneurysmal wall and preventing rupture compared to therapies that solely focus on enhancing EPC numbers.

EPCs can be relatively easily isolated from tissues such as bone marrow or blood in research settings. However, their clinical translation necessitates rigorous manufacturing processes to ensure safety and efficacy: EPCs must be purified from heterogeneous cell populations and expanded under standardized culture conditions. And cells require extensive testing for viability, sterility, genetic stability, and functional potency (e.g., differentiation capacity, cytokine secretion). Clinical-grade EPCs must be produced in Good Manufacturing Practice-certified facilities, adhering to strict protocols for traceability and contamination control. Skilled technicians and quality assurance teams are essential to manage these complex workflows. These challenges underscore the gap between laboratory-scale EPC isolation and scalable clinical production. But multiple studies have confirmed the separation method of EPC and its safe application in clinical practice [130].

For the application of stem cells, preclinical testing using animal models is particularly important because stem cells can function through multiple mechanisms, and it is difficult to predict the situation of stem cells in animals under cell culture conditions. The integration of physiological functions and permanent tissue reconstruction is the goal of stem cell therapy for many diseases. Animal models will help detect potential side effects of transplanted cell products. Animal model testing is particularly necessary when cells undergo extensive in vitro processing and/or when cell products come from pluripotent stem cells. It must be acknowledged that preclinical testing, including animal model studies, can provide limited evidence on the response of human cell transplantation in humans, as cell behavior also depends on the cell environment and the recipient's immune response. The

independent peer review of preclinical data must take into account this uncertainty. Only under the condition that preclinical data has sufficient persuasiveness, can clinical trials be cautiously and progressively conducted on appropriate patients under strict and independent scientific and ethical supervision [131].

According to ISSCR Guidelines for the Clinical Translation of Stem Cells: chemical or recombinant protein products can be produced with high purity, and the cells produced or collected and prepared from different anatomical locations or individuals have outstanding biological diversity issues. In allogeneic treatment, identifying a single source of main cells can reduce this variability. However, the cell sources for autologous therapy are relatively limited, making it impossible to conduct extensive quality testing. Given that researchers generally lack experience in production, cultivation, and use, the definition of the properties and potential of stem cells and their derivatives still needs to be determined in future research processes [132].

Summary

In the field of treatment of intracranial aneurysms, endothelial progenitor cells (EPCs) show unique potential by promoting vascular endothelial repair, inhibiting inflammatory response and regulating vascular remodeling, which provides a new strategy for clinical intervention. However, at present, the application of EPCs still faces many challenges: the limited source of autologous EPCs and the insufficient expansion efficiency in vitro, the low survival rate of transplanted cells and the functional heterogeneity limit its large-scale application; In addition, the dynamic regulation mechanism of EPCs in the complex microenvironment of aneurysms has not been fully clarified, and the long-term efficacy and safety still need more clinical data to support. Future research needs to focus on the unification of separation and identification standards of EPCs, and the development of targeted delivery system based on biomaterials. Only through interdisciplinary collaboration and translational medicine innovation can we break through the existing bottleneck and promote the efficient transformation of EPC therapy from experimental platform to clinical practice.

Abbreviations

BM	Bone Marrow
CXCR-1	Chemokine Receptor 1
ECs	Endothelial Cells
EPCs	Endothelial Progenitor Cells
FD	Flow Diverter
Flt-1	Fms-related receptor tyrosine kinase
H/R	Hypoxia/Reoxygenation
HUVECs	Human Umbilical Vein Endothelial Cells
IA	Intracranial Aneurysm
PECAM-1	Platelet Endothelial Cell Adhesion Molecule-1
PED	Pipeline Flex Embolization Device
PI3K/MAPK	Phosphatidylinositol 3-kinase/ Mitogen-Activated Protein Kinase
PGI2	Prostaglandin-I-2
PSGL-1	P-Selectin Glycoprotein Ligand-1
Rac2	RAS-related C3 botulinum toxin substrate 2
SAH	Subarachnoid Hemorrhage
SDF-1α	Stromal cell-Derived Factor-1 alpha
UEA-1	Ulex Europeus Agglutinin-1
VSMCs	Vascular Smooth Muscle Cells
VTE	Venous Thrombosis

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Data availability

Not applicable.

Declarations

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