Unlocking the potential of endothelial progenitor cells: a comprehensive review of definitions, applications, and future directions

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ABSTRACT

Endothelial progenitor cells (EPCs) are undifferentiated cells with the capacity to mature into endothelial cells (ECs). EPCs have garnered considerable attention in the fields of regenerative medicine and cardiovascular therapy, owing to their pivotal role in neovascularization and vascular repair. Nonetheless, numerous challenges and questions persist regarding the translational research and practical application of EPCs. This review aims to examine the varying definitions of EPCs, their classification, extraction methods, and sources. It will also address the optimization of cultivation techniques for EPCs and the reprogramming of EPCs into induced pluripotent stem cells (iPSCs). Furthermore, the review will delve into the role of EPCs in cardiovascular diseases (CVD), septic shock, and rheumatic immune conditions, as well as their implications in connective tissue diseases (CTDs) and skin soft tissue regeneration. Finally, the article will discuss future research prospects for EPCs, aiming to engage and inspire readers.

Subjects Biochemistry, Biotechnology, Cell Biology, Molecular Biology, Cardiology
Keywords Endothelial progenitor cells, Definitions, Cardiovascular diseases, Septic shock, Rheumatic immune conditions, Connective tissue diseases

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Additional Information and Declarations can be found on page 18

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INTRODUCTION

The discovery of endothelial progenitor cells (EPCs) marked a significant shift in the understanding of vasculogenesis, which was previously thought to occur only during embryogenesis. EPCs were first isolated from human peripheral blood (PB) in 1997, challenging the traditional view and suggesting that these cells could contribute to the repair and regeneration of blood vessels in adults (*Asahara et al., 1997*). EPCs are derived from various sources, including bone marrow, spleen, and umbilical cord, and play a crucial role in the regeneration of the endothelial lining of blood vessels and wound repair. They are believed to originate from hematopoietic stem cells and mesenchymal stem cells,

and their mobilization from bone marrow to peripheral circulation is highly regulated under both normal physiological conditions and stress (*Rana, Kumar & Sharma, 2018*). In addition to EPCs, ECs themselves are diverse and can be classified into different subtypes based on their location and function. Arterial and venous ECs, for instance, exhibit distinct phenotypic and functional characteristics. Arterial ECs are typically exposed to higher shear stress and have a more robust structure compared to venous ECs. The specification of ECs into arterial or venous subtypes is influenced by environmental cues, which can be leveraged to modulate pluripotent stem cell-derived endothelial cells (PSC-ECs) into a more homogeneous phenotype for clinical applications (*Arora, Yim & Toh, 2019*).

The understanding of EPCs and their interaction with different ECs subtypes continues to evolve, with ongoing research focused on elucidating their roles in vascular biology and potential therapeutic applications. Despite the initial enthusiasm, the field has faced challenges, particularly concerning the characterization and standardization of EPCs, as well as their clinical implications (*Resch et al., 2012*). The therapeutic applications of EPCs are also being explored in clinical settings. Strategies such as EPCs infusion therapy and the use of EPCs-capturing stents are being investigated to enhance endothelial repair and improve outcomes in patients with cardiovascular diseases (*Xiao & Kuang, 2021*; *Bianconi et al., 2018a*). However, challenges remain in standardizing EPCs isolation and characterization methods, as well as understanding the optimal conditions for their therapeutic use. Nonetheless, the study of EPCs and ECs remains a promising area of research with the potential to significantly impact cardiovascular therapy and regenerative medicine.

Finally, to enhance our understanding of EPCs, we employ a schematic diagram to visually depict their mechanism of action, angiogenesis processes, and associated signaling pathways (refer to Fig. 1 for further details).

SEARCH METHODOLOGY SECTION

This review is specifically aimed at researchers with a focus on EPCs. We utilized a systematic search methodology for the literature review, which involved the formulation of specific research questions and the establishment of inclusion and exclusion criteria for selecting relevant studies. To ensure the rigor and impartiality of the review, we conducted an exhaustive examination of pertinent literature addressing the research questions. The review is structured into 11 sections, each of which will be independently searched and screened. Figure 2 and Table 1 outline the search strategy employed to identify relevant studies. The search process consisted of four distinct phases of search and refinement and was conducted across major online databases, including IEEE Xplore® (https://ieeexplore.ieee.org), ACM Digital Library, Google Scholar, SpringerLink, and Science Direct.

In Phase 1, the search string detailed in Table 1 was developed to extract pertinent studies from the aforementioned databases. This search string was formulated through an analysis of keywords identified in the relevant literature. Initially, the application of these search terms yielded a substantial number of potential studies within the databases. The

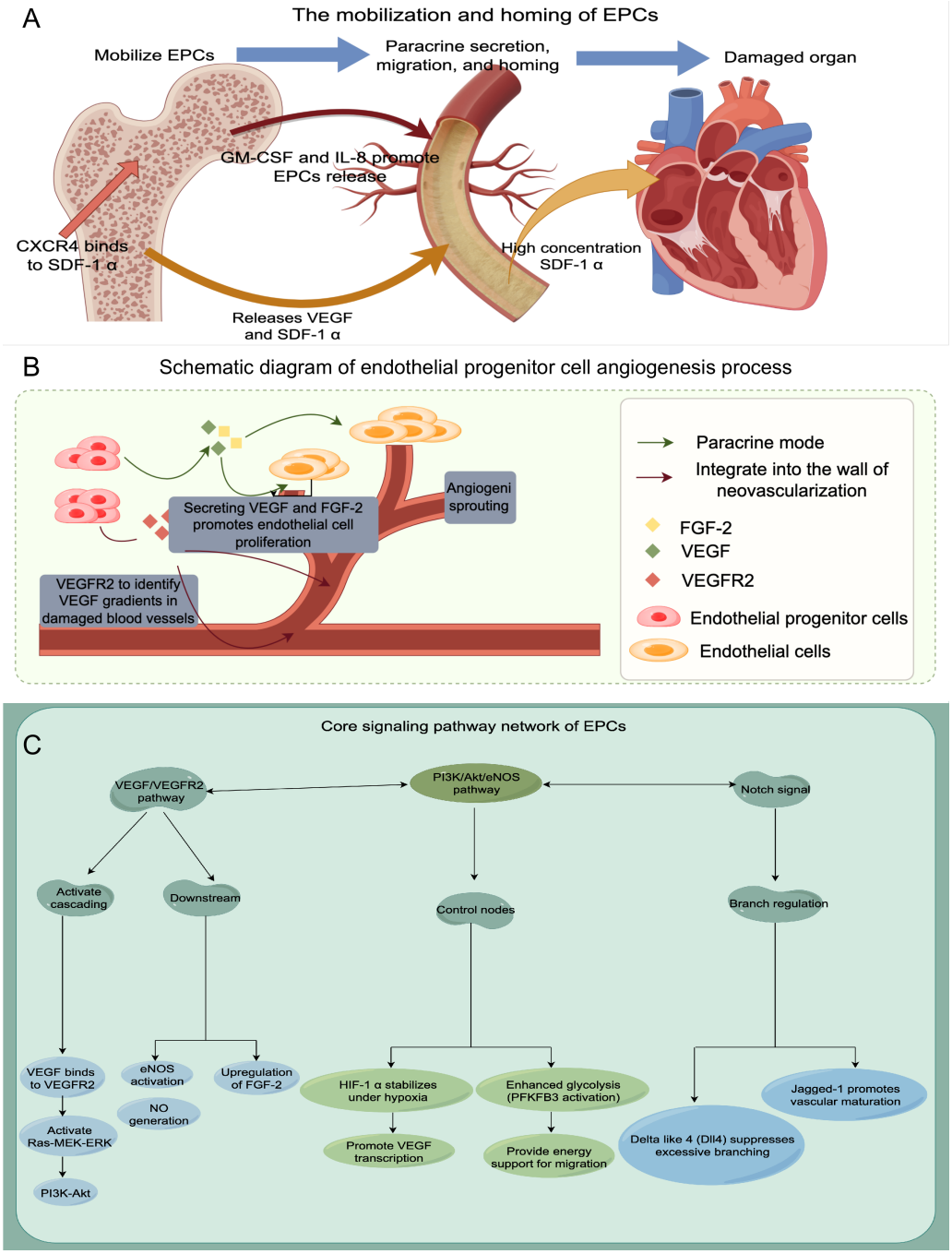

Figure 1 The schematic diagram to visually depict their mechanism of action, angiogenesis processes, and associated signaling pathways. (A) Mobilization and homing of EPCs; (B) Schematic diagram of endothelial progenitor cell angiogenesis process; (C) The signaling pathway network of EPCs.
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specific search strategy and the quantity of literature retrieved are presented in Table 1. In Phase 2, articles were excluded based on unavailability, redundancy, or lack of relevance. In Phase 3, inclusion and exclusion criteria were established to refine the filtering process

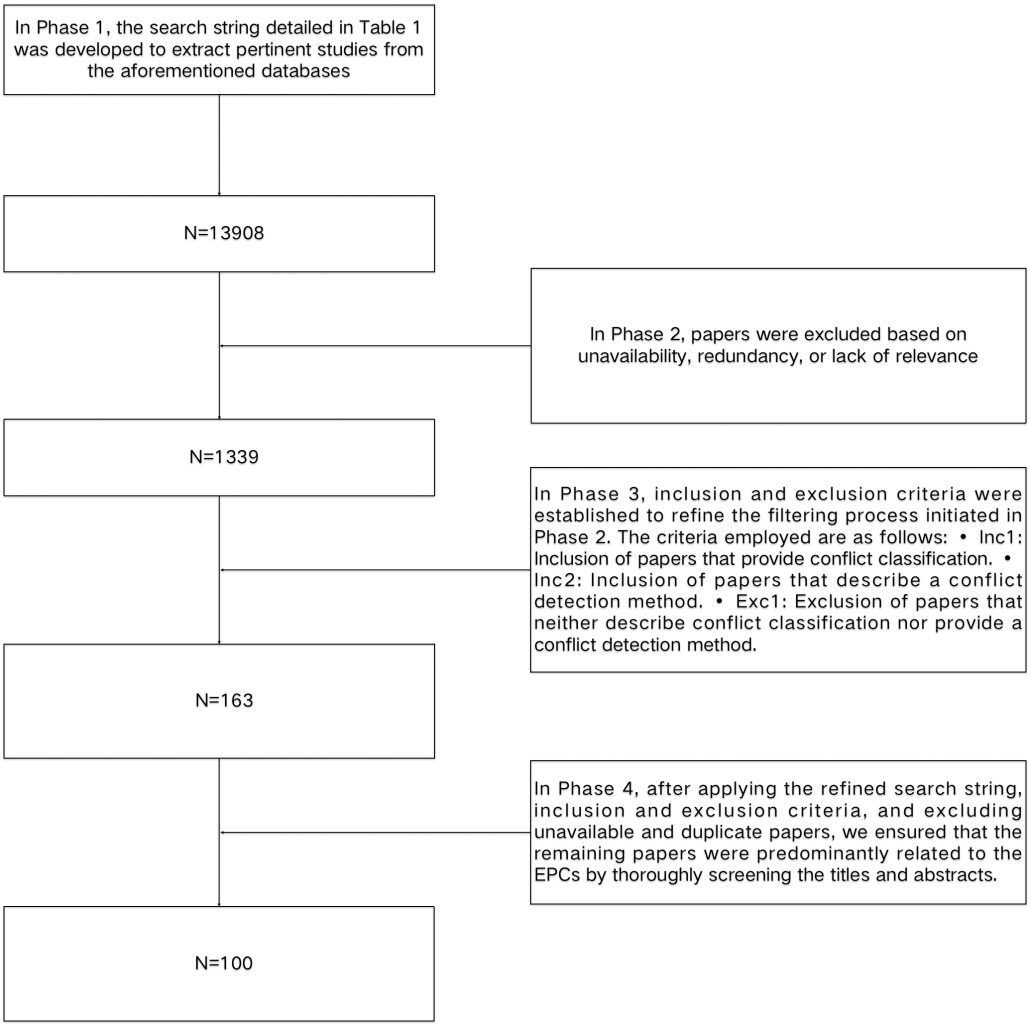

Figure 2 **A flowchart in the Search Methodology section.**

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initiated in Phase 2. The criteria employed are as follows: •Inc1: Inclusion of articles that provide conflict classification. •Inc2: Inclusion of articles that describe a conflict detection method. •Exc1: Exclusion of articles that neither describe conflict classification nor provide a conflict detection method. In Phase 4, after applying the refined search string, inclusion and exclusion criteria, and excluding unavailable and duplicate articles, we ensured that the remaining articles were predominantly related to the EPCs by thoroughly screening the titles and abstracts. Finally, we obtained 86 studies.

Definition and classification of EPCs

EPCs are bone marrow-derived cells crucial for vascular repair and regeneration, circulating in the bloodstream to aid in vasculogenesis and endothelial repair (*Ozkok & Yildiz, 2018*; *Leszczynska et al., 2013*). The definition of EPCs remains debated, with researchers

Table 1 **The survey search methodology.**

	The search string In phase 1	In phase 2	In phase 3	In phase 4
1. Divergence in the definition of EPCs	("EPCs" or "endothelial progenitor cells") and "definition", $N = 200$	$N = 93$	$N = 29$	$N = 23$
2. Early EPCs and late EPCs	("early EPCs" or "late EPCs") and "category", $N = 700$	$N = 270$	$N = 20$	$N = 9$
3. Extraction methods of EPCs	("EPCs" or "endothelial progenitor cells") and "Extraction methods", $N = 109$	$N = 46$	$N = 8$	$N = 5$
4. The sources of EPCs	("EPCs" or "endothelial progenitor cells") and "source", $N = 7220$	$N = 208$	$N = 12$	$N = 4$
5. Optimization of cultivation techniques for EPCs	("EPCs" or "endothelial progenitor cells") and "cultivation", $N = 265$	$N = 103$	$N = 12$	$N = 10$
6. EPCs and CVD	("EPCs" or "endothelial progenitor cells") and "CVD", $N = 233$	$N = 110$	$N = 20$	$N = 9$
7. EPCs and septic shock	("EPCs" or "endothelial progenitor cells") and ("septic shock" or "sepsis"), $N = 96$	$N = 49$	$N = 9$	$N = 8$
8. EPCs and rheumatic immunity, CTDs	("EPCs" or "endothelial progenitor cells") and ("rheumatic immunity" or "CTD"), $N = 50$	$N = 23$	$N = 11$	$N = 5$
9. EPCs and skin soft tissue regeneration	("EPCs" or "endothelial progenitor cells") and ("skin" or "soft tissue") and "regeneration", $N = 4960$	$N = 380$	$N = 22$	$N = 8$
10. Reprogramming of EPCs into iPSCs	("EPCs" or "endothelial progenitor cells") and "iPSCs" and "reprogramming", $N = 52$	$N = 40$	$N = 10$	$N = 11$
11. Research prospect of EPCs	("EPCs" or "endothelial progenitor cells") and "Research prospect", $N = 23$	$N = 17$	$N = 10$	$N = 8$

Notes.
EPCs, endothelial progenitor cells; iPSCs, induced pluripotent stem cells; CVD, cardiovascular disease; CTDs, connective tissue diseases.

advocating for immunophenotyping and functional assays to distinguish different EPCs subtypes (*Markeson et al., 2015*).

Several researchers propose that cells expressing CD34, CD133, and KDR markers, known as $CD34^{+}CD133^{+}KDR^{+}$ triple-positive cells, are categorized as EPCs (*Arica et al., 2019*; *Cesari et al., 2008*). These cells have attracted considerable interest due to their potential to differentiate into mature endothelial cells. Moreover, the functional properties of $CD34^{+}CD133^{+}KDR^{+}$ EPCs are closely linked to their clonogenic potential and angiogenic capabilities. Studies have shown that these cells exhibit high clonogenicity, which is a predictor of their ability to proliferate and form new blood vessels. The initial clonogenic potential of these cells is indicative of their future functionality, suggesting that selecting for high-quality progenitor cells can enhance therapeutic outcomes in ischemic conditions (*Ferratge et al., 2017*; *Atashi et al., 2018*).

Researchers are increasingly focusing on EPCs subpopulations with lineage-negative markers like $CD14^{-}/CD45^{-}$, which may enhance angiogenesis. Studies indicate that EPCs function differently under various pathological conditions. For instance, in emphysema, $CD45^{-}/CD31^{+}/CD34^{+}$ EPCs aid lung endothelial regeneration and angiogenesis (*Pakhomova et al., 2020*). Similarly, in chronic obstructive pulmonary disease (COPD), the drug Spikerone boosts pulmonary microcirculation regeneration by mobilizing $CD45^{-}/CD34^{+}/CD31^{+}$ EPCs (*Skurikhin et al., 2021*). Research indicates that the $CD14^{-}$ subset can form EPCs colonies only when co-cultured with the $CD14^{+}$ subset, implying that $CD14^{-}$ may be the source of EPCs. This colony formation relies on cytokines from the CD14 subset, especially angiopoietin 1, offering new insights into EPCs origins and functions (*Sudchada et al., 2012*). These findings highlight the therapeutic potential of lineage-negative EPCs across different pathological contexts.

Certain studies contend that EPCs have the ability to differentiate into mature endothelial cells exhibiting a "cobble-stone" morphology (*Ni et al., 2019*; *Badawi et al., 2022*). Previous study has corroborated this finding (Fig. 3) (*Ye et al., 2014*). Recent studies have highlighted the importance of the microenvironment in promoting the differentiation of EPCs. For instance, the presence of specific growth factors and extracellular matrix components can significantly enhance the maturation of these cells into functional endothelial cells. The differentiation process transforms these progenitor cells into what can be described as "cobble-stone" in the vascular landscape, contributing to the integrity and functionality of blood vessels. This maturation is not merely a change in morphology but also involves a complex reprogramming of gene expression that equips these cells with the necessary capabilities to participate in angiogenesis and vascular repair (*Plein et al., 2018*; *Kanaya et al., 2015*).

Studies indicate that EPCs can be identified by their uptake of acetylated low density lipoprotein (ac-LDL) and binding to Ulex europaeus agglutinin-1 (UEA-1) (*Ye et al., 2014*; *Wang et al., 2021*; *He et al., 2014*). LDL is vital in cardiovascular health and endothelial function, affecting EPCs, which are important for vascular repair. The interaction between LDL and EPCs, particularly ac-LDL uptake and UEA binding, is crucial for EPCs differentiation and function. EPCs that take up ac-LDL show improved capillary

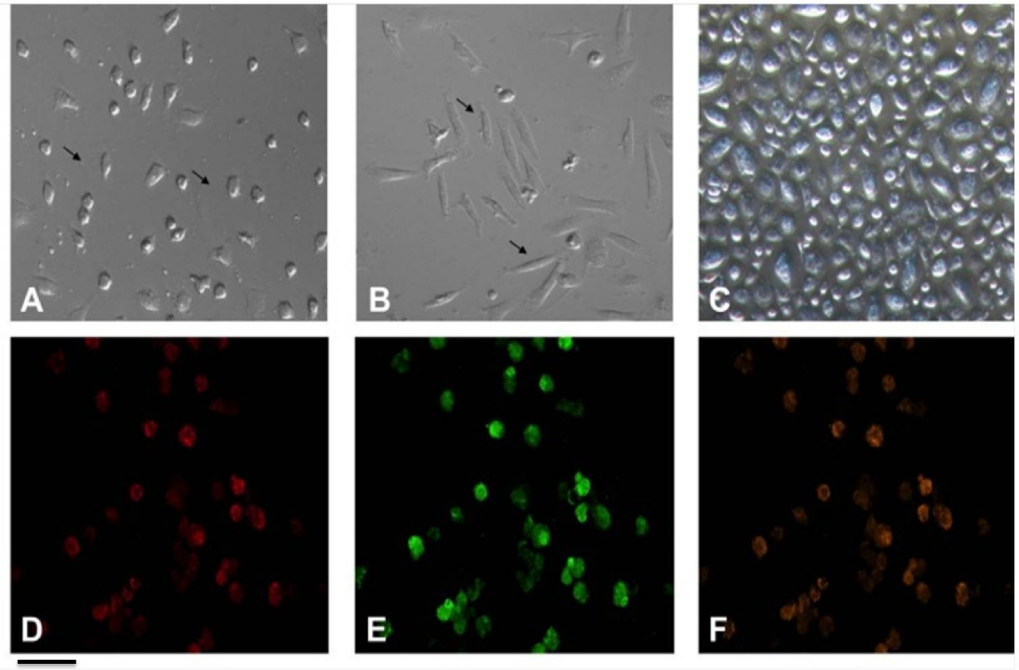

Figure 3 Characterization of EPCs derived from human peripheral blood. (A) The ellipsoid morphology of EPCs derived from human PB on day seven of culture. (B) The spindle-shaped morphology of EPCs derived from human PB on day14 of culture. (C) The ''cobble-stone'' morphology of EPCs derived from human PB on day 21 of culture; (D) fluorescence image shows uptake of DiI-Ac-LDL; (E) fluorescence image demonstrate expression of FITC-UEA lectin in EPCs; (F) all DiI-labeled acetylated LDL(+) cells stained positive for FITC-ulex-lectin binding, as can be seen in overlay. Scale bar: A–F = 100 μm. Adapted from *Ye et al. (2014)*.

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formation, essential for repairing damaged endothelium and restoring vascular function (*Chen et al., 2011*; *Hong et al., 2020*).

Moreover, the binding of UEA to EPCs serves as a marker for identifying these cells and assessing their functionality. UEA binds to specific carbohydrate structures on the surface of endothelial cells, which can be indicative of the cells' maturity and their ability to participate in angiogenesis. The interaction between UEA and EPCs can provide insights into the cellular mechanisms that govern endothelial repair processes, particularly in the context of oxidative stress and inflammation induced by oxidized LDL (ox-LDL) (*Liu, Gao & Wang, 2023*; *Wang et al., 2020*). In addition to their role in vascular repair, the relationship between LDL and EPCs has implications for understanding the pathophysiology of cardiovascular diseases. Elevated levels of LDL, particularly in its oxidized form, are associated with endothelial dysfunction and increased cardiovascular risk. Studies have shown that ox-LDL can impair EPCs function, leading to reduced angiogenic potential and contributing to the progression of atherosclerosis (*Wang et al., 2020*; *Zenti & Stefanutti, 2011*). Therefore, understanding the dynamics of LDL and EPCs interactions is crucial for developing therapeutic strategies aimed at enhancing endothelial repair and mitigating cardiovascular disease risk.

In conclusion, EPCs may not represent a singular cell type; instead, they constitute a heterogeneous group of cells sharing the capacity to differentiate into endothelial cells with angiogenic properties. Classical EPCs are characterized by three primary features: (1) the expression of CD34, CD133, and KDR markers, with the gradual loss of CD133 as the cells mature; (2) the ability to uptake ac-LDL and bind to UEA-I; and (3) the potential to differentiate into mature endothelial cells, which exhibit a characteristic "cobble-stone" morphology.

Early EPCs vs. Late EPCs

EPCs are classified into two main categories: early EPCs and late EPCs, each playing distinct roles in vascular repair and regeneration. Cells identified as $CD34^+KDR^+$ are categorized as late EPCs, while those characterized by the markers $CD34^+CD133^+KDR^+$ are considered early EPCs, as delineated in previous research (*Arica et al., 2019*).

Early EPCs initiate endothelial repair by secreting angiogenic factors and promoting neovascularization through paracrine mechanisms. In contrast, late EPCs excel in proliferation, migration, and differentiation into mature endothelial cells, vital for ongoing vascular repair and maintaining endothelial integrity (*Cheng et al., 2013*; *Tagawa et al., 2015*). These functional differences are reflected in their gene expression: early EPCs express more inflammatory cytokines and paracrine factors to recruit cells to injury sites, while late EPCs have genes linked to proliferation and angiogenesis, aiding in endothelial tubulogenesis and neovascularization (*Ke et al., 2017*; *Li et al., 2012*). This distinction is crucial for vascular repair, especially in conditions like coronary artery disease and ischemic injuries. Research indicates that late EPCs outperform early EPCs in functionality, exhibiting higher proliferation and enhanced tube formation crucial for angiogenesis. These cells express key endothelial markers and aid in blood vessel repair, making them significant in cardiovascular research and therapy (*Fernandez et al., 2014*; *Paschalaki & Randi, 2018*). The differentiation of EPCs into mature endothelial cells is complex, involving multiple factors. Understanding the differences between early and late EPCs and the conditions promoting their maturation is vital for their clinical use, especially in cardiovascular disease and tissue engineering (*Kumboyono et al., 2021*; *Ablin et al., 2011*). Table 2 presents a comparative analysis of the similarities and differences between early EPCs and late EPCs.

In summary, the roles of early and late EPCs in vascular biology are complementary, with early EPCs initiating the repair process and late EPCs ensuring its completion and maintenance.

Sources and extraction methods of EPCs

Various sources of EPCs

The isolation of EPCs can be achieved from multiple sources, including PB, umbilical cord blood (UCB), and bone marrow. Each of these sources presents unique advantages and challenges that can influence the yield and functionality of the isolated EPCs.

PB is often considered a convenient source for EPCs isolation due to its accessibility and the relatively non-invasive nature of collection. Studies have demonstrated that EPCs can be effectively isolated from PB mononuclear cells (PBMCs) using techniques such as

Table 2 Comparative analysis of early EPCs *vs.* late EPCs.

Feature	Early EPCs	Late EPCs
Source	Peripheral blood, bone marrow, monocytes/macrophages	Peripheral blood, bone marrow, umbilical cord blood, vascular endothelia
Culture time	Emerge within 4–7 days	Appear after 2–4 weeks
Morphology	Spindle-shaped	Cobblestone-shaped
Proliferation capacity	Low proliferative potential	High proliferative potential
Surface Markers	$CD34^{+}$, $CD133^{+}$, VEGFR-$^{2+}$, $CD31^{+}$	$CD34^{-}$, $CD133^{-}$, VEGFR-2^{++}, VE-cadherin^{++}, vWF^{++}, $CD146^{+}$
Functional roles	Secrete angiogenic cytokines (VEGF, IL-8), Modulate inflammation	Form vascular networks, Produce NO, Integrate into endothelial layers
Lifespan	Short (3–4 weeks)	Long (up to 12 weeks)
Oxidative stress	Susceptible to oxidative damage	Resistant due to higher eNOS and SOD activity
Therapeutic use	Cytokine secretion for paracrine effects	Neovascularization via direct endothelial integration
Clinical relevance	Associated with acute vascular repair	Linked to chronic vascular remodeling

Notes.
Table 2 presents a comparative analysis of the similarities and differences between early EPCs and late EPCs.

density gradient centrifugation. However, the overall number of EPCs obtained from PB may be limited compared to other sources. Studies have shown that the culture conditions, such as the type of substrate and the presence of growth factors like vascular endothelial growth factor (VEGF), can significantly affect the yield and functionality of the EPCs obtained. For instance, a study demonstrated that culturing PBMCs on fibronectin in the presence of high VEGF concentrations resulted in improved EPCs proliferation and differentiation compared to other substrates and conditions (*Wu et al., 2012*).

UCB is another promising source for EPCs. It is rich in hematopoietic stem cells and has been shown to contain a substantial population of EPCs. The advantages of using UCB include its availability and the ethical considerations surrounding its collection, as it is obtained after childbirth without harm to the donor. Research indicates that UCB-derived EPCs exhibit robust proliferative capacity and can effectively contribute to vascular repair (*Phuc et al., 2012*). Furthermore, studies have highlighted the potential of UCB to yield multiple types of stem cells, including hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), which can be beneficial for various regenerative therapies (*Bhartiya et al., 2012*).

Bone marrow remains a traditional source for EPCs isolation, particularly in clinical settings. Bone marrow-derived EPCs have been extensively studied for their role in neovascularization and tissue repair. The isolation process typically involves aspiration and subsequent processing to obtain mononuclear cells, which can then be cultured to enrich for EPCs. While bone marrow-derived EPCs have demonstrated significant regenerative potential, the invasive nature of bone marrow collection and the associated risks can limit its use in some patient populations (*Jin et al., 2014*).

In summary, while PB, UCB, and bone marrow each serve as viable sources for EPCs isolation, the choice of source may depend on specific clinical needs, the desired quantity of cells, and the associated ethical considerations.

Extraction methods

EPCs are vital for vascular repair and regeneration, and isolating them is key for therapeutic uses. The immunomagnetic bead method, which uses antibodies on magnetic beads to capture EPCs, ensures high purity and viability, making it popular in regenerative medicine. Another common technique is density gradient centrifugation, which separates cells based on density. This method effectively isolates PBMCs for further EPCs extraction, enhancing cell recovery and reducing contamination (*Papadimitriou et al., 1996*; *Belkhir et al., 2016*). Combining immunomagnetic bead methods with density gradient centrifugation improves EPCs isolation efficiency. Initially, density gradient centrifugation enriches PBMCs, followed by immunomagnetic separation to specifically isolate EPCs. This two-step process enhances EPCs purity and functionality, crucial for cell therapy and tissue engineering applications (*Fu et al., 2017*).

Fluorescence-activated cell sorting (FACS) is a crucial technique in cell biology for precisely sorting and analyzing cell types, including EPCs, based on specific markers. It is invaluable for studying EPCs and has diverse applications, such as isolating circulating tumor cells (CTCs) with minimal contamination by combining immunomagnetic enrichment with FACS. This method highlights FACS's versatility in isolating rare cell populations for molecular analyses (*Say et al., 2013*). Additionally, FACS is used to study dendritic cell subsets in human atherosclerotic plaques, emphasizing its role in identifying immune cells in complex samples (*Magbanua & Park, 2013*).

Optimization of EPCs cultivation techniques

The cultivation of EPCs represents a pivotal area of research. Numerous studies have investigated diverse methodologies to enhance the proliferation and functionality of EPCs, emphasizing the significance of scaffold materials, growth factors, and culture conditions. These cultivation techniques are applicable across all EPCs subtypes, including endothelial colony-forming cells (ECFCs), early and late EPCs.

One significant advancement in EPCs cultivation is the use of specific scaffolds that enhance cell adhesion and proliferation. For instance, a study demonstrated that EPCs could be effectively cultivated on β-tricalcium phosphate (β-TCP) granules without the need for fibronectin coating, which is traditionally used to improve cell attachment. This research indicated that the design of the scaffold significantly influences cell behavior, with structural differences affecting both adherence and metabolic activity of EPCs (*Störmann et al., 2019*). Additionally, the incorporation of growth factors such as erythropoietin and granulocyte-monocyte colony-stimulating factor has been shown to further enhance the proliferation and differentiation of EPCs when cultured on fibrin scaffolds (*Grieb et al., 2011*).

The choice of culture media plays a pivotal role in the success of EPCs cultivation. A comparative analysis of various endothelial cell culture media revealed that defined media containing specific growth factors like EGF, FGF2, and VEGF significantly improved the outgrowth and viability of endothelial cells derived from both UCB and PB (*Ye et al., 2014*; *Leopold et al., 2019*). This finding underscores the necessity of selecting appropriate culture conditions to maximize the yield and functionality of EPCs. Another innovative approach involves the use of human platelet lysate as a substitute for animal serum in the culture of

ECFCs. This method not only adheres to good manufacturing practices but also enhances cell viability and proliferation rates, making it a promising technique for clinical applications (*Denecke et al., 2015*). Long-term culture of endothelial progenitor-like cells from adipose-derived stem cells in endothelial growth media can cause significant morphological and functional changes, suggesting their potential in vascular repair (*Amerion et al., 2018*). Recent studies have explored the molecular mechanisms of EPCs function, showing that inhibiting glycogen synthase kinase 3β boosts EPCs proliferation and migration in hypercholesterolemic conditions, and PDGFR-β phosphorylation is linked to their angiogenic potential. These findings emphasize the role of signaling pathways in enhancing EPCs therapeutic efficacy (*Cui et al., 2015*; *Lu et al., 2017*).

Purifying high-purity EPCs is essential for effective research and therapy. Methods like FACS and two-dimensional preparative chromatography have shown promise. FACS isolates specific cell populations using fluorescence, while chromatography, using novel polar copolymerized RP stationary phases, achieves high purity and recovery from complex mixtures. Both techniques offer advantages for EPCs purification (*Larcher et al., 2018*; *Jin et al., 2013*). The development of a high-resolution purification method for CD34-negative severe combined immune deficiency (SCID)-repopulating cells from human cord blood, using monoclonal antibodies and fluorescence-activated cell sorting, offers valuable techniques for EPCs purification (*Ishii et al., 2011*). These methods, initially designed for other cells, can be adapted to improve the purity and consistency of EPCs for research and clinical use.

Overall, the cultivation techniques for EPCs are rapidly evolving, with ongoing research aimed at optimizing conditions to enhance their regenerative capabilities. The integration of advanced scaffolding materials, growth factor supplementation, and molecular targeting strategies holds promise for improving the efficacy of EPCs in clinical settings, particularly in the treatment of ischemic diseases and tissue regeneration.

EPCs in regenerative medicine and disease treatment

The use of EPCs in clinical settings involves several key conditions and considerations: source of EPCs, characterization and purification, clinical Indications, delivery methods, safety and efficacy. Understanding EPCs biology is essential, as they aid in re-endothelialization and neovascularization, crucial for tissue repair and vascular health. Despite interest, progress is hindered by EPCs population heterogeneity and the absence of standardized isolation and expansion methods (*Wang et al., 2013*; *Keighron et al., 2018*). Identifying specific EPCs subtypes, like ECFCs, which have shown positive effects in preclinical studies, is crucial (*Keighron et al., 2018*). A key factor is optimizing EPCs delivery and function. Strategies like genetic modifications and co-culturing with other cells, such as bone marrow-derived mesenchymal stem cells (BMSCs), can enhance EPCs efficacy by promoting angiogenesis and improving outcomes in conditions like intrauterine adhesion (*Yu et al., 2018*). However, clinical application faces challenges such as cell survival, integration, and risks of adverse effects. Innovative tissue-engineered carrier matrices may help overcome these issues by supporting EPCs survival and growth (*Balaji et al., 2013*).

EPCs and cardiovascular disease

EPCs have emerged as critical players in the context of cardiovascular disease (CVD), particularly due to their role in vascular repair and regeneration. These cells, which are derived from the bone marrow, are mobilized into the bloodstream in response to vascular injury and are essential for maintaining endothelial integrity. Their functionality and numbers are often compromised in patients with various cardiovascular risk factors, leading to impaired vascular repair mechanisms and contributing to the progression of CVD (*Madonna, Novo & Balistreri, 2016*; *Lorenzen et al., 2010*).

Circulating endothelial progenitor cells (cEPCs) are a type of undifferentiated cells derived from bone marrow or vascular walls, with the potential to differentiate into mature endothelial cells and migrate to PB under physiological or pathological stimuli, participating in angiogenesis and injury repair. Research indicates that fewer cEPCs increase cardiovascular event risks like heart attacks and strokes (*Lorenzen et al., 2010*). Studies show that patients with chronic kidney disease and plaque psoriasis have lower EPCs levels linked to higher cardiovascular risks, influenced by inflammation and endothelial dysfunction (*Michalska et al., 2020*). These conditions impair EPCs function *via* pathways like NF-κB, NLRP3, and p38 MAPK. However, small molecule inhibitors and activators can restore EPCs activity by managing oxidative stress, inflammation, and metabolic reprogramming. Future research should focus on targeted delivery and multi-target strategies to boost EPCs' therapeutic potential in vascular repair.

The therapeutic potential of EPCs has been widely studied, with human embryonic stem cells (hESCs) being differentiated into EPCs that are vital for vascular repair. Generating EPCs with specific phenotypes is crucial for cardiovascular therapies, as they aid in re-endothelialization and neo-vascularization. EPCs from hPSCs express functional receptors like TLR4, which boosts their proliferation and maintains their stem cell characteristics, increasing their availability for therapeutic applications (*He et al., 2010*). Using hPSCs enables the study of new signaling pathways and molecular mechanisms to boost EPCs functionality. Activating pathways like AKT can enhance EPCs migration and tube formation, crucial for vascular repair. This understanding may lead to targeted therapies that enhance EPCs-based treatments' effectiveness (*Hu et al., 2015*). Furthermore, the role of EPCs as biomarkers for cardiovascular risk has gained attention. Studies have indicated that low levels of circulating EPCs are predictive of adverse cardiovascular outcomes, including mortality (*Rigato, Avogaro & Fadini, 2016*). Previous study found that decreased EPCs levels, particularly within the $CD34^+/CD133^+/KDR^+$ cell subsets, were linked to higher mortality rates in patients experiencing acute myocardial infarction (AMI) (Table 3) (*Ye et al., 2023*). This underscores the potential of using EPCs counts as a clinical tool for assessing cardiovascular risk and guiding therapeutic strategies.

In conclusion, EPCs play a pivotal role in cardiovascular health, serving both as a marker of vascular integrity and a potential therapeutic target. Their involvement in the pathophysiology of cardiovascular disease emphasizes the need for further research to fully understand their mechanisms and to develop effective strategies for enhancing their function in clinical settings (*Ye et al., 2023*; *Balistreri et al., 2015*; *Chiva-Blanch et al., 2014*).

Table 3 Comparison of EPCs between survival group and death group in AMI patients ($M \pm SD$).

The category	Survival group ($N = 68$)	Death group ($N = 23$)	$t/U/x^2$	P
$CD34^+/CD133^+$ cells (%)	0.50 ± 0.17	0.37 ± 0.18	19.56	0.00
$CD34^+/CD133^+/KDR^+$ EPCs (%)	0.19 ± 0.06	0.14 ± 0.02	28.96	0.00

Notes.
A statistically significant increases counts $CD34^+/CD133^+/KDR^+$ EPCs were observed in the survival group compared with the death group in AMI patients ($P < 0{:}05$). Adapted from *Ye et al. (2023)*.

EPCs and septic shock

EPCs are crucial in septic shock for vascular repair and maintaining endothelial integrity. Sepsis triggers systemic inflammation, causing endothelial dysfunction and leading to multiple organ dysfunction syndrome (MODS) with high mortality rates. The correlation between organ failures and mortality is crucial for assessing patient outcomes. Research indicates that mortality risk escalates with more organ failures. For example, a study on critically ill patients revealed a 25% overall mortality rate, which rose sharply with each additional organ failure, underscoring the severe effect of multiple organ dysfunctions on survival (*Yasumoto et al., 1994*). EPCs mobilization and function are vital for reducing sepsis effects and aiding recovery from endothelial damage. Recent studies have highlighted the relationship between circulating EPCs levels and the severity of septic shock. For instance, research indicates that patients with septic shock exhibit altered levels of circulating EPCs, which are associated with the clinical course of the disease. Specifically, higher levels of circulating EPCs have been observed in patients with less severe forms of sepsis, while those with more severe septic shock show diminished EPCs mobilization and function (*Krautkrämer et al., 2014*; *Liu et al., 2018*). This suggests that the ability of EPCs to respond to endothelial injury is compromised in severe cases, potentially exacerbating the condition. The therapeutic potential of EPCs in septic shock has been explored through various interventions aimed at enhancing their mobilization and function. For example, the administration of specific growth factors has been shown to increase EPCs levels in circulation, which may aid in re-endothelialization and restoration of vascular integrity (*De Biasi et al., 2015*; *Edwards et al., 2018*). Additionally, the paracrine effects of EPCs, mediated through the release of microvesicles containing pro-angiogenic factors, have been implicated in promoting endothelial repair and reducing inflammation during septic episodes (*Zhang, Malik & Rehman, 2014*; *Hubert et al., 2014*).

The interplay between EPCs and the inflammatory milieu in septic shock is complex. Neutrophils, which are often activated during sepsis, can influence EPCs behavior by enhancing their angiogenic properties and promoting their recruitment to sites of injury. However, excessive inflammation may also hinder EPCs function, leading to impaired endothelial repair mechanisms. This dual role of EPCs as both protectors and potential victims of the inflammatory response underscores the need for targeted therapeutic strategies that can enhance their beneficial effects while mitigating the adverse impacts of sepsis-induced inflammation (*Li et al., 2012*; *Hubert et al., 2014*).

In summary, EPCs play a pivotal role in the pathophysiology of septic shock, with their levels and functionality serving as important indicators of disease severity and recovery potential.

EPCs in rheumatic immunity and connective tissue diseases

The relationship between EPCs and rheumatic immunity, particularly in the context of connective tissue diseases (CTDs), is an area of growing interest in the field of immunology and rheumatology. EPCs are crucial for the maintenance and repair of the endothelium, and their dysfunction has been implicated in various autoimmune conditions, including systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). In patients with these diseases, an imbalance between endothelial injury and repair mechanisms can lead to significant cardiovascular complications, which are prevalent in this population. In a study focusing on polymyalgia rheumatica (PMR), researchers found that patients exhibited a marked increase in circulating endothelial microparticles (EMPs) and a decrease in EPCs, indicating a state of endothelial dysfunction. This imbalance was closely associated with systemic inflammation, as evidenced by elevated C-reactive protein (CRP) levels. Notably, treatment with corticosteroids resulted in a significant reduction of both CRP and the EMP/EPCs ratio, suggesting that controlling inflammation can restore some degree of endothelial repair capacity in these patients (*Pirro et al., 2012*).

Moreover, the role of EPCs extends beyond mere repair; they are also involved in the modulation of immune responses. In the context of autoimmune diseases, the dysregulation of EPCs function may contribute to the chronic inflammatory state observed in conditions like rheumatoid arthritis (RA) and SLE. The presence of autoantibodies and inflammatory cytokines can adversely affect EPCs mobilization and function, leading to impaired angiogenesis and further exacerbating vascular complications associated with these diseases (*Arida et al., 2018*; *Zanatta et al., 2019*). Research has also indicated that the therapeutic targeting of EPCs could represent a novel approach in managing cardiovascular risks in patients with rheumatic diseases. For instance, interventions aimed at enhancing EPCs mobilization or function may help mitigate the vascular damage that often accompanies chronic inflammation in CTDs. This is particularly relevant given the established link between inflammation and accelerated atherosclerosis in these patients, which underscores the need for integrated management strategies that address both autoimmune and cardiovascular aspects of care (*Chen et al., 2021*; *Santos-Moreno et al., 2021*).

In conclusion, the interplay between EPCs and rheumatic immunity highlights a critical area of research that could lead to improved therapeutic strategies for patients with CTDs. Understanding the mechanisms that govern EPCs function in the context of autoimmunity will be essential for developing targeted interventions that can enhance endothelial repair and reduce cardiovascular morbidity in this vulnerable population.

EPCs in skin and soft tissue regeneration

EPCs play a crucial role in the regeneration of skin soft tissues, particularly in the context of wound healing and tissue engineering. These cells are essential for the formation of new blood vessels, a process known as angiogenesis, which is vital for supplying nutrients and oxygen to regenerating tissues. Recent studies have highlighted the significance of EPCs

in enhancing the vascularization of engineered skin substitutes, thereby improving their integration and functionality when applied to full-thickness skin defects. For instance, the incorporation of EPCs into dermal scaffolds has been shown to significantly increase microvessel density and promote collagen synthesis, which are critical factors for effective skin regeneration (*Auxenfans et al., 2012*; *Meruane, Rojas & Marcelain, 2012*). In the realm of ear reconstruction, the application of EPCs has shown promising results. The regeneration of auricular structures requires not only the restoration of skin but also the re-establishment of vascular networks to support the newly formed tissue. Research indicates that EPCs can enhance the vascularization of auricular scaffolds, thereby improving the overall success of ear reconstruction procedures. By promoting angiogenesis, EPCs facilitate the integration of engineered tissues with the host vasculature, which is essential for the survival and functionality of the reconstructed ear (*Frueh et al., 2017*; *Otto et al., 2022*).

The combination of EPCs with other cell types, such as adipose-derived stem cells (ASCs) and fibroblasts, has been explored to further enhance tissue regeneration. This synergistic approach not only improves the vascular supply but also supports the structural integrity and functional recovery of the engineered tissues. For example, studies have demonstrated that the co-culture of EPCs with ASCs leads to improved outcomes in skin regeneration, as these cells work together to create a more favorable microenvironment for healing (*Patschan et al., 2016*; *Jeon, Joo & Cha, 2020*). The potential of using EPCs in tissue engineering extends beyond skin and ear reconstruction. Their ability to promote angiogenesis and support tissue regeneration makes them a valuable component in various regenerative medicine applications. As research continues to uncover the mechanisms by which EPCs contribute to tissue healing, their incorporation into engineered constructs is likely to become a standard practice in the field of regenerative medicine (*Cheung et al., 2014*; *Goyer et al., 2019*).

In conclusion, EPCs are pivotal in the regeneration of skin soft tissues and ear reconstruction. Their role in enhancing vascularization and supporting the integration of engineered tissues underscores their importance in advancing tissue engineering strategies. Future studies focusing on optimizing the use of EPCs in conjunction with other regenerative cell types will likely lead to improved outcomes in the treatment of complex wounds and reconstructive surgeries.

Future research directions for EPCs

Reprogramming of EPCs into induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) are a type of pluripotent stem cell that can be generated directly from adult cells. They are remarkable because they possess the ability to differentiate into almost any cell type, similar to embryonic stem cells, but without the associated ethical concerns. This capability makes iPSCs a powerful tool for regenerative medicine, disease modeling, and drug screening. The process of reprogramming somatic cells to become iPSCs involves the introduction of specific transcription factors, which effectively "reset" the cell's identity to a pluripotent state (*Chari & Mao, 2016*; *Menon et al., 2016*). The conversion of EPCs into iPSCs is intriguing as it demonstrates cellular reprogramming's flexibility and potential. EPCs, crucial for blood vessel repair, can be

reprogrammed into iPSCs, broadening their applications. This process highlights iPSCs' versatility and offers new research and treatment possibilities, especially for vascular diseases and regenerative medicine (*Orqueda, Giménez & Pereyra-Bonnet, 2016*; *Polanco, Kuang & Yoon, 2020*).

To transform somatic cells into pluripotent ones, specific transcription factors like the Yamanaka factors (Oct4, Sox2, Klf4, and c-Myc) can be used to reprogram cells such as fibroblasts and EPCs into iPSCs (*Xie et al., 2014*). This reversion to pluripotency allows cells to differentiate into various lineages, including endothelial cells, essential for vascular repair. Additionally, the microenvironment, enhanced by biomaterials and growth factors, plays a crucial role in cell fate decisions and can improve reprogramming efficiency by influencing EPCs' differentiation or reprogramming pathways (*Rahman et al., 2010*; *Farkas et al., 2020*).

Researches on deriving EPCs from hESCs and/or human iPSCs are vital for regenerative medicine and vascular biology. Effective differentiation protocols are essential. One approach uses high-capacity helper-dependent adenoviral vectors (HDAdVs) for precise gene targeting without DNA breaks, facilitating accurate gene knockout and knock-in (*Aizawa et al., 2012*). Another promising method employs zinc-finger nucleases (ZFNs) for precise genome editing, allowing for the creation of lineage-specific reporters and gene expression modification to guide stem cell differentiation. This precise editing is crucial for directing stem cells into EPCs (*Hockemeyer et al., 2009*). Furthermore, the implications of successfully reprogramming EPCs to iPSCs extend beyond basic research. This capability could lead to advancements in personalized medicine, where patient-derived cells can be used to model diseases, screen drugs, and develop tailored therapies. The potential to generate a renewable source of endothelial cells from iPSCs derived from EPCs could also address the challenges associated with cell scarcity in transplantation therapies (*Ge et al., 2018*; *Eminli et al., 2021*).

Reprogramming EPCs into iPSCs using small molecules like CHIR99021, RepSox, VPA, Forskolin, 616452, and BIX-01294 marks a significant advance in stem cell research and regenerative medicine. This approach, which also involves transcription factors and engineered microenvironments, holds potential for innovative therapies in treating vascular diseases and advancing regenerative medicine.

Research prospect of EPCs

The discussion on EPCs applications and future directions is an evolving field of research that holds significant promise for advancing medical science, particularly in the areas of regenerative medicine and vascular biology. EPCs are known for their potential to contribute to the repair and regeneration of damaged blood vessels, making them a focal point in studies related to cardiovascular diseases, wound healing, and tissue engineering. The research surrounding EPCs has expanded to explore their mechanisms of action, functional characteristics, and potential clinical applications, particularly in the context of ischemic diseases and cardiovascular disorders.

The signaling pathways that regulate EPCs function are also a focus of current research. Calcium signaling, for example, has been shown to play a pivotal role in EPCs proliferation

and migration, with store-operated calcium entry being a critical mechanism driving these processes (*Moccia et al., 2014*). Additionally, the dysregulation of signaling pathways, such as the CXCR4/JAK-2 pathway, has been implicated in impairing the angiogenic capacity of EPCs, particularly in models of ischemic disease (*Cheng et al., 2019*). Understanding these pathways could lead to novel therapeutic strategies aimed at enhancing EPCs function and improving outcomes in patients with cardiovascular diseases. Moreover, the paracrine effects of EPCs are gaining recognition as a vital aspect of their therapeutic potential. EPCs secrete a variety of growth factors and cytokines that can promote tissue repair and regeneration. For instance, the secretion of VEGF and other angiogenic factors has been shown to enhance the survival and function of surrounding cells, including cardiomyocytes, in ischemic conditions (*Hong et al., 2021*; *Zhao et al., 2018*). This paracrine signaling mechanism underscores the importance of EPCs not only as direct contributors to neovascularization but also as modulators of the local microenvironment. In addition to their roles in cardiovascular repair, EPCs have been implicated in various pathological conditions, including COPD and cancer. Research has indicated that EPCs populations may be altered in these diseases, affecting their functionality and contributing to disease progression (*Bianconi et al., 2018b*). This highlights the need for further studies to elucidate the relationship between EPCs and different disease states, as well as their potential as biomarkers for disease prediction and progression.

EPCs-based therapies have gained attention for their potential in treating vascular conditions, particularly ischemic issues like myocardial injury. A study demonstrated that using superparamagnetic iron oxide (SPIO) nanoparticle-conjugated CD34 antibodies can enhance EPCs recruitment to ischemic areas, improving heart revascularization (*Sun et al., 2022*). Besides heart conditions, EPCs therapies show promise in treating diabetes-related vascular dysfunction by aiding endothelial repair and mitigating complications (*Georgescu et al., 2011*). The combined use of EPCs transplantation and simvastatin has been studied for improving angiogenesis and reducing apoptosis in ischemic conditions. In a mouse model of hindlimb ischemia, this combination significantly improved blood flow and capillary density, while decreasing muscle cell apoptosis. This indicates that EPCs paired with other therapies can boost vascular repair and regeneration (*Hu et al., 2008*).

In conclusion, the research prospect of EPCs is vast and multifaceted, encompassing their roles in vascular biology, mechanisms of action, and therapeutic applications. Continued exploration of EPCs biology, including their signaling pathways, paracrine functions, and interactions with other cell types, will be essential for harnessing their full potential in regenerative medicine and improving cardiovascular health.

CONCLUSION

Research on EPCs is gaining attention, particularly in relation to angiogenesis and endothelial lesions. However, challenges like unclear differentiation, low mobilization, and clinical translation difficulties persist. Future efforts should integrate omics technologies and standardized training to advance from basic research to precision treatment. This review aims to provide a comprehensive understanding of EPCs and highlight the challenges in their research.

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Author Contributions

- Gongjie Ye conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Yongfei Song conceived and designed the experiments, performed the experiments, prepared figures and/or tables, and approved the final draft.
- Yiru Weng performed the experiments, prepared figures and/or tables, and approved the final draft.
- Jiangfang Lian analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Jianqing Zhou performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
- Zhouzhou Dong conceived and designed the experiments, analyzed the data, authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

This is a literature review.

REFERENCES

Ablin JN, Boguslavski V, Aloush V, Elkayam O, Paran D, Levartovski D, Caspi D, George J. 2011. Enhanced adhesive properties of endothelial progenitor cells (EPCs) in patients with SLE. *Rheumatology International* **31(6)**:773–778 DOI 10.1007/s00296-010-1377-6.

Aizawa E, Hirabayashi Y, Iwanaga Y, Suzuki K, Sakurai K, Shimoji M, Aiba K, Wada T, Tooi N, Kawase E, Suemori H, Nakatsuji N, Mitani K. 2012. Efficient and accurate homologous recombination in hESCs and hiPSCs using helper-dependent adenoviral vectors. *Molecular Therapy* **20(2)**:424–431 DOI 10.1038/mt.2011.266.

Amerion M, Valojerdi MR, Abroun S, Totonchi M. 2018. Long term culture and differentiation of endothelial progenitor like cells from rat adipose derived stem cells. *Cytotechnology* **70**:397–413 DOI 10.1007/s10616-017-0155-7.

Arica DA, Akşan B, Örem A, Altinkaynak BA, Yayli S, Sönmez M. 2019. High levels of endothelial progenitor cells and circulating endothelial cells in patients with Behçet's disease and their relationship to disease activity. *Anais Brasileiros de Dermatologia* **94(3)**:320–326 DOI 10.1590/abd1806-4841.20198169.

Arida A, Protogerou AD, Kitas GD, Sfikakis PP. 2018. Systemic inflammatory response and atherosclerosis: the paradigm of chronic inflammatory rheumatic diseases. *International Journal of Molecular Sciences* **19(7)**:1890 DOI 10.3390/ijms19071890.

Arora S, Yim EKF, Toh YC. 2019. Environmental specification of pluripotent stem cell derived endothelial cells toward arterial and venous subtypes. *Frontiers in Bioengineering and Biotechnology* **7**:143 DOI 10.3389/fbioe.2019.00143.

Asahara T, Murohara T, Sullivan A, Silver M, Van der Zee R, Li T, Witzenbichler B, Schatteman G, Isner JM. 1997. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* **275(5302)**:964 DOI 10.1126/science.275.5302.964.

Atashi A, Islami M, Mortazavi Y, Soleimani M. 2018. Homing genes expression in fucosyltransferase VI-treated umbilical cord blood CD133+ cells which expanded on protein-coated nanoscaffolds. *Molecular Biotechnology* **60(7)**:455–467 DOI 10.1007/s12033-018-0086-3.

Auxenfans C, Lequeux C, Perrusel E, Mojallal A, Kinikoglu B, Damour O. 2012. Adipose-derived stem cells (ASCs) as a source of endothelial cells in the reconstruction of endothelialized skin equivalents. *Journal of Tissue Engineering and Regenerative Medicine* **6(7)**:512–518 DOI 10.1002/term.454.

Badawi A, Jefferson OC, Huuskes BM, Ricardo SD, Kerr PG, Samuel CS, Murthi P. 2022. A novel approach to enhance the regenerative potential of circulating endothelial progenitor cells in patients with end-stage kidney disease. *Biomedicines* **10(4)**:883 DOI 10.3390/biomedicines10040883.

Balaji S, King A, Crombleholme TM, Keswani SG. 2013. The role of endothelial progenitor cells in postnatal vasculogenesis: implications for therapeutic neovascularization and wound healing. *Advances in Wound Care (New Rochelle)* **2(6)**:283–295 DOI 10.1089/wound.2012.0398.

Balistreri CR, Buffa S, Pisano C, Lio D, Ruvolo G, Mazzesi G. 2015. Are endothelial progenitor cells the real solution for cardiovascular diseases? Focus on controversies and perspectives. *BioMed Research International* **2015**:835934 DOI 10.1155/2015/835934.

Belkhir L, De Laveleye M, Vandercam B, Zech F, Delongie KA, Capron A, Yombi J, Vincent A, Elens L, Haufroid V. 2016. Quantification of darunavir and etravirine in human peripheral blood mononuclear cells using high performance liquid chromatography tandem mass spectrometry (LC-MS/MS), clinical application in a cohort of 110 HIV-1 infected patients and evidence of a potential drug-drug interaction. *Clinical Biochemistry* **49(7–8)**:580–586 DOI 10.1016/j.clinbiochem.2015.12.011.

Bhartiya D, Shaikh A, Nagvenkar P, Kasiviswanathan S, Pethe P, Pawani H, Mohanty S, Rao SG, Zaveri K, Hinduja I. 2012. Very small embryonic-like stem cells with

maximum regenerative potential get discarded during cord blood banking and bone marrow processing for autologous stem cell therapy. *Stem Cells and Development* **21**(**1**):1–6 DOI 10.1089/scd.2011.0311.

Bianconi V, Sahebkar A, Kovanen P, Bagaglia F, Ricciuti B, Calabrò P, Patti G, Pirro M. 2018a. Endothelial and cardiac progenitor cells for cardiovascular repair: a controversial paradigm in cell therapy. *Pharmacology and Therapeutics* **181**:156–168 DOI 10.1016/j.pharmthera.2017.08.004.

Bianconi V, Sahebkar A, Kovanen P, Bagaglia F, Ricciuti B, Calabrò P, Patti G, Pirro M. 2018b. Endothelial and cardiac progenitor cells for cardiovascular repair: a controversial paradigm in cell therapy. *Pharmacology and Therapeutics* **181**:156–168 DOI 10.1016/j.pharmthera.2017.08.004.

Cesari F, Caporale R, Marcucci R, Caciolli S, Stefano PL, Capalbo A, Macchi C, Vannucci M, Gensini GF, Abbate R, Gori AM. 2008. NT-proBNP and the anti-inflammatory cytokines are correlated with endothelial progenitor cells' response to cardiac surgery. *Atherosclerosis* **199**(**1**):138–146 DOI 10.1016/j.atherosclerosis.2007.09.045.

Chari S, Mao S. 2016. Timeline: iPSCs—the first decade. *Cell* **164**(**3**):580 DOI 10.1016/j.cell.2016.01.023.

Chen DY, Sawamura T, Dixon RAF, Sánchez-Quesada JL, Chen CH. 2021. Autoimmune rheumatic diseases: an update on the role of atherogenic electronegative LDL and potential therapeutic strategies. *Journal of Clinical Medicine* **10**(**9**):1992 DOI 10.3390/jcm10091992.

Chen R, Yu H, Jia ZY, Yao QL, Teng GJ. 2011. Efficient nano iron particle-labeling and noninvasive MR imaging of mouse bone marrow-derived endothelial progenitor cells. *International Journal of Nanomedicine* **6**:511–519 DOI 10.2147/IJN.S16934.

Cheng CC, Chang SJ, Chueh YN, Huang TS, Huang PH, Cheng SM, Tsai TN, Chen JW, Wang HW. 2013. Distinct angiogenesis roles and surface markers of early and late endothelial progenitor cells revealed by functional group analyses. *BMC Genomics* **14**:182 DOI 10.1186/1471-2164-14-182.

Cheng LM, Li YJ, Chen XF, Li XL, Chen XS, Du YH. 2019. ClC-3 deficiency impairs the neovascularization capacity of early endothelial progenitor cells by decreasing CXCR4/JAK-2 signalling. *Canadian Journal of Cardiology* **35**(**11**):1546–1556 DOI 10.1016/j.cjca.2019.08.009.

Cheung HK, Han TT, Marecak DM, Watkins JF, Amsden BG, Flynn LE. 2014. Composite hydrogel scaffolds incorporating decellularized adipose tissue for soft tissue engineering with adipose-derived stem cells. *Biomaterials* **35**(**6**):1914–1923 DOI 10.1016/j.biomaterials.2013.11.067.

Chiva-Blanch G, Condines X, Magraner E, Roth I, Valderas-Martínez P, Arranz S, Casas R, Martínez-Huélamo M, Vallverdú-Queralt A, Quifer-Rada P, Lamuela-Raventos RM, Estruch R. 2014. The non-alcoholic fraction of beer increases stromal cell derived factor 1 and the number of circulating endothelial progenitor cells in high cardiovascular risk subjects: a randomized clinical trial. *Atherosclerosis* **233**(**2**):518–524 DOI 10.1016/j.atherosclerosis.2013.12.048.

Cui B, Jin J, Ding X, Deng M, Yu S, Song M, Yu Y, Zhao X, Chen J, Huang L. 2015. Glycogen synthase kinase 3β inhibition enhanced proliferation, migration and functional re-endothelialization of endothelial progenitor cells in hypercholesterolemia microenvironment. *Experimental Biology and Medicine (Maywood)* **240(12)**:1752–1763 DOI 10.1177/1535370215589908.

De Biasi S, Cerri S, Bianchini E, Gibellini L, Persiani E, Montanari G, Luppi F, Carbonelli CM, Zucchi L, Bocchino M, Zamparelli AS, Vancheri C, Sgalla G, Richeldi L, Cossarizza A. 2015. Levels of circulating endothelial cells are low in idiopathic pulmonary fibrosis and are further reduced by anti-fibrotic treatments. *BMC Medicine* **13**:277 DOI 10.1186/s12916-015-0515-0.

Denecke B, Horsch LD, Radtke S, Fischer JC, Horn PA, Giebel B. 2015. Human endothelial colony-forming cells expanded with an improved protocol are a useful endothelial cell source for scaffold-based tissue engineering. *Journal of Tissue Engineering and Regenerative Medicine* **9(11)**:E84–E97 DOI 10.1002/term.1673.

Edwards N, Langford-Smith AWW, Wilkinson FL, Alexander MY. 2018. Endothelial progenitor cells: new targets for therapeutics for inflammatory conditions with high cardiovascular risk. *Frontiers in Medicine (Lausanne)* **5**:200 DOI 10.3389/fmed.2018.00200.

Eminli S, Kwieder B, Yi K, Huang CJZ, Moon JI, Chang CH, Kiskin FN, Morrell NW, Hamilton B, Rana AA. 2021. Clinically compatible advances in blood-derived endothelial progenitor cell isolation and reprogramming for translational applications. *New Biotechnology* **63**:1–9 DOI 10.1016/j.nbt.2021.02.001.

Farkas S, Simara P, Rehakova D, Veverkova L, Koutna I. 2020. Endothelial progenitor cells produced from human pluripotent stem cells by a synergistic combination of cytokines, small compounds, and serum-free medium. *Frontiers in Cell and Developmental Biology* **8**:309 DOI 10.3389/fcell.2020.00309.

Fernandez CE, Obi-onuoha IC, Wallace CS, Satterwhite LL, Truskey GA, Reichert WM. 2014. Late-outgrowth endothelial progenitors from patients with coronary artery disease: endothelialization of confluent stromal cell layers. *Acta Biomaterialia* **10(2)**:893–900 DOI 10.1016/j.actbio.2013.10.004.

Ferratge S, Ha G, Carpentier G, Arouche N, Bascetin R, Muller L, Germain S, Uzan G. 2017. Initial clonogenic potential of human endothelial progenitor cells is predictive of their further properties and establishes a functional hierarchy related to immaturity. *Stem Cell Research* **21**:148–159 DOI 10.1016/j.scr.2017.04.009.

Frueh FS, Später T, Lindenblatt N, Calcagni M, Giovanoli P, Scheuer C, Menger MD, Laschke MW. 2017. Adipose tissue-derived microvascular fragments improve vascularization, lymphangiogenesis, and integration of dermal skin substitutes. *Journal of Investigative Dermatology* **137(1)**:217–227 DOI 10.1016/j.jid.2016.08.010.

Fu RQ, Hu DP, Hu YB, Hong L, Sun QF, Ding JG. 2017. miR-21 promotes α-SMA and collagen I expression in hepatic stellate cells *via* the Smad7 signaling pathway. *Molecular Medicine Reports* **16(4)**:4327–4333 DOI 10.3892/mmr.2017.7054.

Ge Q, Zhang H, Hou J, Wan L, Cheng W, Wang X, Dong D, Chen C, Xia J, Guo J, Chen X, Wu X. 2018. VEGF secreted by mesenchymal stem cells mediates the differentiation of endothelial progenitor cells into endothelial cells *via* paracrine mechanisms. *Molecular Medicine Reports* **17**:1667–1675 DOI 10.3892/mmr.2017.8059.

Georgescu A, Alexandru N, Constantinescu A, Titorencu I, Popov D. 2011. The promise of EPCs-based therapies on vascular dysfunction in diabetes. *European Journal of Pharmacology* **669(1–3)**:1–6 DOI 10.1016/j.ejphar.2011.07.035.

Goyer B, Larouche D, Kim DH, Veillette N, Pruneau V, Bernier V, Auger FA, Germain L. 2019. Immune tolerance of tissue-engineered skin produced with allogeneic or xenogeneic fibroblasts and syngeneic keratinocytes grafted on mice. *Acta Biomaterialia* **90**:192–204 DOI 10.1016/j.actbio.2019.04.010.

Grieb G, Simons D, Steinberger H, Vollmar A, Bernhagen J, Pallua N. 2011. Improved *in vitro* cultivation of endothelial progenitor cells as basis for dermal substitutes with enhanced angiogenic capabilities. *Langenbeck's Archives of Surgery* **396(8)**:1255–1262 DOI 10.1007/s00423-011-0839-y.

He ZH, Chen P, Chen Y, Zhu YQ, He SD, Ye JR, Liu D, Yang Y. 2014. Dual effects of cigarette smoke extract on proliferation of endothelial progenitor cells and the protective effect of 5-aza-2'-deoxycytidine on EPCs against the damage caused by CSE. *BioMed Research International* **2014**:640752 DOI 10.1155/2014/640752.

He J, Xiao Z, Chen X, Chen M, Fang L, Yang M, Lv Q, Li Y, Li G, Hu J, Xie X. 2010. The expression of functional Toll-like receptor 4 is associated with proliferation and maintenance of stem cell phenotype in endothelial progenitor cells (EPCs). *Journal of Cellular Biochemistry* **111(1)**:179–186 DOI 10.1002/jcb.22686.

Hockemeyer D, Soldner F, Beard C, Gao Q, Mitalipova M, De Kelver RC, Katibah GE, Amora R, Boydston EA, Zeitler B, Meng X, Miller JC, Zhang L, Rebar EJ, Gregory PD, Urnov FD, Jaenisch R. 2009. Efficient targeting of expressed and silent genes in human ESCs and iPSCs using zinc-finger nucleases. *Nature Biotechnology* **27(9)**:851–857 DOI 10.1038/nbt.1562.

Hong X, Oh N, Wang K, Neumeyer J, Lee CN, Lin RZ, Piekarski B, Emani S, Greene AK, Friehs I, Del Nido PJ, Melero-Martin JM. 2021. Human endothelial colony-forming cells provide trophic support for pluripotent stem cell-derived cardiomyocytes *via* distinctively high expression of neuregulin-1. *Angiogenesis* **24(2)**:327–344 DOI 10.1007/s10456-020-09765-3.

Hong Y, Yu Q, Kong Z, Wang M, Zhang R, Li Y, Liu Y. 2020. Exogenous endothelial progenitor cells reached the deficient region of acute cerebral ischemia rats to improve functional recovery *via* Bcl-2. *Cardiovascular Diagnosis and Therapy* **10(4)**:695–704 DOI 10.21037/cdt-20-329.

Hu N, Kong LS, Chen H, Li WD, Qian AM, Wang XY, Du XL, Li CL, Yu XB, Li XQ. 2015. Autophagy protein 5 enhances the function of rat EPCs and promotes EPCs homing and thrombus recanalization *via* activating AKT. *Thrombosis Research* **136(3)**:642–651 DOI 10.1016/j.thromres.2015.06.038.

Hu Z, Zhang F, Yang Z, Yang N, Zhang D, Zhang J, Cao K. 2008. Combination of simvastatin administration and EPCs transplantation enhances angiogenesis and

protects against apoptosis for hindlimb ischemia. *Journal of Biomedical Science* **15(4)**:509–517 DOI 10.1007/s11373-008-9243-1.

Hubert L, Darbousset R, Panicot-Dubois L, Robert S, Sabatier F, Fallague K, Dignat-George F, Dubois C. 2014. Neutrophils recruit and activate human endothelial colony-forming cells at the site of vessel injury *via* P-selectin glycoprotein ligand-1 and L-selectin. *Journal of Thrombosis and Haemostasis* **12(7)**:1170–1181 DOI 10.1111/jth.12551.

Ishii M, Matsuoka Y, Sasaki Y, Nakatsuka R, Takahashi M, Nakamoto T, Yasuda K, Matsui K, Asano H, Uemura Y, Tsuji T, Fukuhara S, Sonoda Y. 2011. Development of a high-resolution purification method for precise functional characterization of primitive human cord blood-derived CD34-negative SCID-repopulating cells. *Experimental Hematology* **39(2)**:203–213 DOI 10.1016/j.exphem.2010.11.008.

Jeon EY, Joo KI, Cha HJ. 2020. Body temperature-activated protein-based injectable adhesive hydrogel incorporated with decellularized adipose extracellular matrix for tissue-specific regenerative stem cell therapy. *Acta Biomaterialia* **114**:244–255 DOI 10.1016/j.actbio.2020.07.033.

Jin H, Kim HS, Kim S, Kim HO. 2014. Erythropoietic potential of CD34+ hematopoietic stem cells from human cord blood and G-CSF-mobilized peripheral blood. *BioMed Research International* **2014**:435215 DOI 10.1155/2014/435215.

Jin H, Liu Y, Feng J, Guo Z, Wang C, Zhong Z, Peng X, Dang J, Tao Y, Liang X. 2013. Efficient purification of high-purity compounds from the stem of Lonicera japonica Thunb using two-dimensional preparative chromatography. *Journal of Separation Science* **36(15)**:2414–2420 DOI 10.1002/jssc.201300319.

Kanaya K, Ii M, Okazaki T, Nakamura T, Horii-Komatsu M, Alev C, Akimaru H, Kawamoto A, Akashi H, Tanaka H, Asahi M, Asahara T. 2015. Sonic Hedgehog signaling regulates vascular differentiation and function in human CD34 positive cells: vasculogenic CD34(+) cells with Sonic Hedgehog. *Stem Cell Research* **14(2)**:165–176 DOI 10.1016/j.scr.2015.01.003.

Ke X, Yang D, Liang J, Wang X, Wu S, Wang X, Hu C. 2017. Human endothelial progenitor cell-derived exosomes increase proliferation and angiogenesis in cardiac fibroblasts by promoting the mesenchymal-endothelial transition and reducing high mobility group box 1 protein B1 expression. *DNA and Cell Biology* **36(11)**:1018–1028 DOI 10.1089/dna.2017.3836.

Keighron C, Lyons CJ, Creane M, O'Brien T, Liew A. 2018. Recent advances in endothelial progenitor cells toward their use in clinical translation. *Frontiers in Medicine (Lausanne)* **5**:354 DOI 10.3389/fmed.2018.00354.

Krautkrämer E, Grouls S, Hettwer D, Rafat N, Tönshoff B, Zeier M. 2014. Mobilization of circulating endothelial progenitor cells correlates with the clinical course of hantavirus disease. *Journal of Virology* **88(1)**:483–489 DOI 10.1128/JVI.02063-13.

Kumboyono K, Chomsy IN, Nurwidyaningtyas W, Cesa FY, Tjahjono CT, Wihastuti TA. 2021. Differences in senescence of late endothelial progenitor cells in non-smokers and smokers. *Tobacco Induced Diseases* **19**:10 DOI 10.18332/tid/135320.

Larcher V, Kunderfranco P, Vacchiano M, Carullo P, Erreni M, Salamon I, Colombo FS, Lugli E, Mazzola M, Anselmo A, Condorelli G. 2018. An autofluorescence-based method for the isolation of highly purified ventricular cardiomyocytes. *Cardiovascular Research* **114**(**3**):409–416 DOI 10.1093/cvr/cvx239.

Leopold B, Strutz J, Weiß E, Gindlhuber J, Birner-Gruenberger R, Hackl H, Appel HM, Cvitic S, Hiden U. 2019. Outgrowth, proliferation, viability, angiogenesis and phenotype of primary human endothelial cells in different purchasable endothelial culture media: feed wisely. *Histochemistry and Cell Biology* **152**(**5**):377–390 DOI 10.1007/s00418-019-01815-2.

Leszczynska J, Zyzynska-Granica B, Koziak K, Ruminski S, Lewandowska-Szumiel M. 2013. Contribution of endothelial cells to human bone-derived cells expansion in co-culture. *Tissue Engineering Part A* **19**(**3–4**):393–402 DOI 10.1089/ten.TEA.2011.0710.

Li H, Zhang X, Guan X, Cui X, Wang Y, Chu H, Cheng M. 2012. Advanced glycation end products impair the migration, adhesion and secretion potentials of late endothelial progenitor cells. *Cardiovascular Diabetology* **11**:46 DOI 10.1186/1475-2840-11-46.

Liu F, Gao B, Wang Y. 2023. CircIRAK1 aggravates ox-LDL-induced endothelial cell injury in atherosclerosis *via* TRIM14 upregulation by binding to miR-330-5p. *Clinical Hemorheology and Microcirculation* **85**(**3**):195–209 DOI 10.3233/CH-221551.

Liu J, Zou GJ, Yang L, Rong S, Li BQ, Tong ZH, Li WQ, Li JS. 2018. Early prediction of persistent organ failure by circulating endothelial progenitor cells in patients with acute pancreatitis. *Shock* **50**(**3**):265–272 DOI 10.1097/SHK.0000000000001065.

Lorenzen J, David S, Bahlmann FH, De Groot K, Bahlmann E, Kielstein JT, Haller H, Fliser D. 2010. Endothelial progenitor cells and cardiovascular events in patients with chronic kidney disease—a prospective follow-up study. *PLOS ONE* **5**(**7**):e11477 DOI 10.1371/journal.pone.0011477.

Lu H, Mei H, Wang F, Zhao Q, Wang S, Liu L, Cheng L. 2017. Decreased phosphorylation of PDGFR-β impairs the angiogenic potential of expanded endothelial progenitor cells *via* the inhibition of PI3K/Akt signaling. *International Journal of Molecular Medicine* **39**(**6**):1492–1504 DOI 10.3892/ijmm.2017.2976.

Madonna R, Novo G, Balistreri CR. 2016. Cellular and molecular basis of the imbalance between vascular damage and repair in ageing and age-related diseases: as biomarkers and targets for new treatments. *Mechanisms of Ageing and Development* **159**:22–30 DOI 10.1016/j.mad.2016.03.005.

Magbanua MJ, Park JW. 2013. Isolation of circulating tumor cells by immunomagnetic enrichment and fluorescence-activated cell sorting (IE/FACS) for molecular profiling. *Methods* **64**(**2**):114–118 DOI 10.1016/j.ymeth.2013.07.029.

Markeson D, Pleat JM, Sharpe JR, Harris AL, Seifalian AM, Watt SM. 2015. Scarring, stem cells, scaffolds and skin repair. *Journal of Tissue Engineering and Regenerative Medicine* **9**(**6**):649–668 DOI 10.1002/term.1841.

Menon S, Shailendra S, Renda A, Longaker M, Quarto N. 2016. An overview of direct somatic reprogramming: the ins and outs of iPSCs. *International Journal of Molecular Sciences* **17**(**1**):141 DOI 10.3390/ijms17010141.

Meruane MA, Rojas M, Marcelain K. 2012. The use of adipose tissue-derived stem cells within a dermal substitute improves skin regeneration by increasing neoangiogenesis and collagen synthesis. *Plastic and Reconstructive Surgery* **130(1)**:53–63 DOI 10.1097/PRS.0b013e3182547e04.

Michalska A, Teichman R, Kręcisz B, Siudak Z, Stępień R, Sadowski M. 2020. Cardiovascular risk in patients with plaque psoriasis and psoriatic arthritis without a clinically overt cardiovascular disease: the role of endothelial progenitor cells. *Postepy Dermatologii I Alergologii* **37(3)**:299–305 DOI 10.5114/ada.2020.96085.

Moccia F, Lodola F, Dragoni S, Bonetti E, Bottino C, Guerra G, Laforenza U, Rosti V, Tanzi F. 2014. Ca2+ signalling in endothelial progenitor cells: a novel means to improve cell-based therapy and impair tumour vascularisation. *Current Vascular Pharmacology* **12(1)**:87–105 DOI 10.2174/15701611120114032716285 8.

Ni HZ, Liu Z, Sun LL, Zhou M, Liu C, Li WD, Li XQ. 2019. Metformin inhibits angiogenesis of endothelial progenitor cells *via* miR-221-mediated p27 expression and autophagy. *Future Medicinal Chemistry* **11(17)**:2263–2272 DOI 10.4155/fmc-2019-0017.

Orqueda AJ, Giménez CA, Pereyra-Bonnet F. 2016. iPSCs: a minireview from bench to bed, including organoids and the CRISPR system. *Stem Cells International* **2016**:5934782 DOI 10.1155/2016/5934782.

Otto IA, Bernal PN, Rikkers M, Van Rijen MHP, Mensinga A, Kon M, Breugem CC, Levato R, Malda J. 2022. Human adult, pediatric and microtia auricular cartilage harbor fibronectin-adhering progenitor cells with regenerative ear reconstruction potential. *IScience* **25(9)**:104979 DOI 10.1016/j.isci.2022.104979.

Ozkok A, Yildiz A. 2018. Endothelial progenitor cells and kidney diseases. *Kidney and Blood Pressure Research* **43(3)**:701–718 DOI 10.1159/000489745.

Pakhomova AV, Pershina OV, Ermakova NN, Krupin VA, Pan ES, Putrova OD, Khmelevskaya ES, Vaizova OE, Pozdeeva AS, Dygai AM, Skurikhin EG. 2020. Pericytes and smooth muscle cells circulating in the blood as markers of impaired angiogenesis during combined metabolic impairments and lung emphysema. *Bulletin of Experimental Biology and Medicine* **168(3)**:334–340 DOI 10.1007/s10517-020-04703-1.

Papadimitriou C, Roots A, Koenigsmann M, Oelmann E, Topp M, Oberberg D, Reufi B, Thiel E, Berdel W. 1996. Fresh peripheral blood mononuclear cell preparations are a better starting material than bone marrow after cryopreservation for immunomagnetic harvesting of CD34(+) hematopoietic cells. *International Journal of Oncology* **9(6)**:1107–1112 DOI 10.3892/ijo.9.6.1107.

Paschalaki KE, Randi AM. 2018. Recent advances in endothelial colony forming cells toward their use in clinical translation. *Frontiers in Medicine (Lausanne)* **5**:295 DOI 10.3389/fmed.2018.00295.

Patschan S, Tampe D, Müller C, Seitz C, Herink C, Müller GA, Zeisberg E, Zeisberg M, Henze E, Patschan D. 2016. Early endothelial progenitor cells (eEPCs) in systemic sclerosis (SSc)—dynamics of cellular regeneration and mesenchymal transdifferentiation. *BMC Musculoskeletal Disorders* **17**:339 DOI 10.1186/s12891-016-1197-2.

Phuc PV, Ngoc VB, Lam DH, Tam NT, Viet PQ, Ngoc PK. 2012. Isolation of three important types of stem cells from the same samples of banked umbilical cord blood. *Cell Tissue Bank* **13(2)**:341–351 DOI 10.1007/s10561-011-9262-4.

Pirro M, Bocci EB, Di Filippo F, Schillaci G, Mannarino MR, Bagaglia F, Gerli R, Mannarino E. 2012. Imbalance between endothelial injury and repair in patients with polymyalgia rheumatica: improvement with corticosteroid treatment. *Journal of Internal Medicine* **272(2)**:177–184 DOI 10.1111/j.1365-2796.2011.02510.x.

Plein A, Fantin A, Denti L, Pollard JW, Ruhrberg C. 2018. Erythro-myeloid progenitors contribute endothelial cells to blood vessels. *Nature* **562(7726)**:223–228 DOI 10.1038/s41586-018-0552-x.

Polanco A, Kuang B, Yoon S. 2020. Bioprocess technologies that preserve the quality of iPSCs. *Trends in Biotechnology* **38(10)**:1128–1140 DOI 10.1016/j.tibtech.2020.03.006.

Rahman N, Purpura KA, Wylie RG, Zandstra PW, Shoichet MS. 2010. The use of vascular endothelial growth factor functionalized agarose to guide pluripotent stem cell aggregates toward blood progenitor cells. *Biomaterials* **31(32)**:8262–8270 DOI 10.1016/j.biomaterials.2010.07.040.

Rana D, Kumar A, Sharma S. 2018. Endothelial progenitor cells as molecular targets in vascular senescence and repair. *Current Stem Cell Research & Therapy* **13(6)**:438–446 DOI 10.2174/1574888X13666180502100620.

Resch T, Pircher A, Kähler CM, Pratschke J, Hilbe W. 2012. Endothelial progenitor cells: current issues on characterization and challenging clinical applications. *Stem Cell Reviews and Reports* **8(3)**:926–939 DOI 10.1007/s12015-011-9332-9.

Rigato M, Avogaro A, Fadini GP. 2016. Levels of circulating progenitor cells, cardiovascular outcomes and death: a meta-analysis of prospective observational studies. *Circulation Research* **118(12)**:1930–1939 DOI 10.1161/CIRCRESAHA.116.308366.

Santos-Moreno P, Burgos-Angulo G, Martinez-Ceballos MA, Pizano A, Echeverri D, Bautista-Niño PK, Roks AJM, Rojas-Villarraga A. 2021. Inflammaging as a link between autoimmunity and cardiovascular disease: the case of rheumatoid arthritis. *RMD Open* **7(1)**:e001470 DOI 10.1136/rmdopen-2020-001470.

Say EA, Melamud A, Esserman DA, Povsic TJ, Chavala SH. 2013. Comparative analysis of circulating endothelial progenitor cells in age-related macular degeneration patients using automated rare cell analysis (ARCA) and fluorescence activated cell sorting (FACS). *PLOS ONE* **8(1)**:e55079 DOI 10.1371/journal.pone.0055079.

Skurikhin E, Pershina O, Zhukova M, Widera D, Pan E, Pakhomova A, Krupin V, Ermakova N, Skurikhina V, Sandrikina L, Morozov S, Kubatiev A, Dygai A. 2021. Spiperone stimulates regeneration in pulmonary endothelium damaged by cigarette smoke and lipopolysaccharide. *International Journal of Chronic Obstructive Pulmonary Disease* **16**:3575–3591 DOI 10.2147/COPD.S336410.

Störmann P, Kupsch J, Kontradowitz K, Leiblein M, Verboket R, Seebach C, Marzi I, Henrich D, Nau C. 2019. Cultivation of EPCs and co-cultivation with MSC on β-TCP granules *in vitro* is feasible without fibronectin coating but influenced by scaffolds' design. *European Journal of Trauma and Emergency Surgery* **45(3)**:527–538 DOI 10.1007/s00068-018-0935-6.

Sudchada S, Kheolamai P, U-Pratya Y, Chayosumrit M, Supokawej A, Manochantr S, Tantrawatpan C, Sritanaudomchai H, Issaragrisil S. 2012. CD14-/CD34+ is the founding population of umbilical cord blood-derived endothelial progenitor cells and angiogenin1 is an important factor promoting the colony formation. *Annals of Hematology* **91(3)**:321–329 DOI 10.1007/s00277-011-1303-3.

Sun R, Wang X, Nie Y, Hu A, Liu H, Zhang K, Zhang L, Wu Q, Li K, Liu C, Zhang H, Zheng B, Li H, Xu H, Xu R, Fu H, Dai L, Jin R, Guo Y. 2022. Targeted trapping of endogenous endothelial progenitor cells for myocardial ischemic injury repair through neutrophil-mediated SPIO nanoparticle-conjugated CD34 antibody delivery and imaging. *Acta Biomaterialia* **146**:421–433 DOI 10.1016/j.actbio.2022.05.003.

Tagawa S, Nakanishi C, Mori M, Yoshimuta T, Yoshida S, Shimojima M, Yokawa J, Kawashiri MA, Yamagishi M, Hayashi K. 2015. Determination of early and late endothelial progenitor cells in peripheral circulation and their clinical association with coronary artery disease. *International Journal of Vascular Medicine* **2015**:674213 DOI 10.1155/2015/674213.

Wang A, Dai L, Zhang N, Lin J, Chen G, Zuo Y, Li H, Wang Y, Meng X, Wang Y. 2020. Oxidized low-density lipoprotein (LDL) and LDL cholesterol are associated with outcomes of minor stroke and TIA. *Atherosclerosis* **297**:74–80 DOI 10.1016/j.atherosclerosis.2020.02.003.

Wang CH, Huang PH, Chen JW, Lin SJ, Lee MF, Yang NI, Cherng WJ. 2013. Clinical application of endothelial progenitor cell: are we ready? *Acta Cardiologica Sinica* **29(6)**:479–487.

Wang M, Li Y, Zhang R, Zhang S, Feng H, Kong Z, Aiziretiaili N, Luo Z, Cai Q, Hong Y, Liu Y. 2021. Adiponectin-transfected endothelial progenitor cells have protective effects after 2-hour middle-cerebral artery occlusion in rats with type 2 diabetes mellitus. *Frontiers in Neurology* **12**:630681 DOI 10.3389/fneur.2021.630681.

Wu YT, Li JX, Liu S, Xin Y, Wang ZJ, Gao J, Ji BY, Fan XM, Zhou QW. 2012. A novel and feasible way to cultivate and purify endothelial progenitor cells from bone marrow of children with congenital heart diseases. *Chinese Medical Journal (Engl)* **125(11)**:1903–1907 DOI 10.3760/cma.j.issn.0366-6999.2012.11.012.

Xiao ST, Kuang CY. 2021. Endothelial progenitor cells and coronary artery disease: current concepts and future research directions. *World Journal of Clinical Cases* **9(30)**:8953–8966 DOI 10.12998/wjcc.v9.i30.8953.

Xie B, Wang J, Liu S, Wang J, Xue B, Li J, Wei R, Zhao Y, Liu Z. 2014. Positive correlation between the efficiency of induced pluripotent stem cells and the development rate of nuclear transfer embryos when the same porcine embryonic fibroblast lines are used as donor cells. *Cell Reprogram* **16(3)**:206–214 DOI 10.1089/cell.2013.0080.

Yasumoto M, Okamoto K, Sato T, Kurose M, Kukita I, Morioka T. 1994. Prognosis of critically ill patients with multiple organ failure. *Journal of Anesthesia* **8(3)**:269–273 DOI 10.1007/BF02514648.

Ye G, Chen X, Zhou Y, Zhou J, Song Y, Yang X, Yang L. 2023. Prognostic value of endothelial progenitor cells in acute myocardial infarction patients. *Mediators of Inflammation* **2023**:4450772 DOI 10.1155/2023/4450772.

Ye G, Guan H, Karush J, Wang F, Xu X, Mao H, Huang X, Yang X, Peng P, Ba Y, Zhou J, Lian J. 2014. Effects of Ca2+-activated potassium and inward rectifier potassium channel on the differentiation of endothelial progenitor cells from human peripheral blood. *Molecular Biology Reports* **41(5)**:3413–3423 DOI 10.1007/s11033-014-3203-9.

Yu J, Jiang L, Gao Y, Sun Q, Liu B, Hu Y, Han X. 2018. Interaction between BMSCs and EPCs promotes IUA angiogenesis *via* modulating PI3K/Akt/Cox2 axis. *American Journal of Translational Research* **10(12)**:4280–4289.

Zanatta E, Colombo C, D'Amico G, d'Humières T, Dal Lin C, Tona F. 2019. Inflammation and coronary microvascular dysfunction in autoimmune rheumatic diseases. *International Journal of Molecular Sciences* **20(22)**:5563 DOI 10.3390/ijms20225563.

Zenti MG, Stefanutti C. 2011. Effects of selective H.E.L.P. LDL-apheresis on plasma inflammatory markers concentration in severe dyslipidemia: implication for anti-inflammatory response. *Cytokine* **56(3)**:850–854 DOI 10.1016/j.cyto.2011.08.038.

Zhang M, Malik AB, Rehman J. 2014. Endothelial progenitor cells and vascular repair. *Current Opinions in Hematology* **21(3)**:224–228 DOI 10.1097/MOH.0000000000000041.

Zhao Y, Song J, Bi X, Gao J, Shen Z, Zhu J, Fu G. 2018. Thymosin β4 promotes endothelial progenitor cell angiogenesis *via* a vascular endothelial growth factor-dependent mechanism. *Molecular Medicine Reports* **18(2)**:2314–2320 DOI 10.3892/mmr.2018.9199.