



Endothelial progenitor cells as the target for cardiovascular disease prediction, personalized prevention, and treatments: progressing beyond the state-of-the-art

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Abstract

Stimulated by the leading mortalities of cardiovascular diseases (CVDs), various types of cardiovascular biomaterials have been widely investigated in the past few decades. Although great therapeutic effects can be achieved by bare metal stents (BMS) and drug-eluting stents (DES) within months or years, the long-term complications such as late thrombosis and restenosis have limited their further applications. It is well accepted that rapid endothelialization is a promising approach to eliminate these complications. Convincing evidence has shown that endothelial progenitor cells (EPCs) could be mobilized into the damaged vascular sites systemically and achieve endothelial repair in situ, which significantly contributes to the re-endothelialization process. Therefore, how to effectively capture EPCs via specific molecules immobilized on biomaterials is an important point to achieve rapid endothelialization. Further, in the context of predictive, preventive, personalized medicine (PPPM), the abnormal number alteration of EPCs in circulating blood and certain inflammation responses can also serve as important indicators for predicting and preventing early cardiovascular disease. In this contribution, we mainly focused on the following sections: the definition and classification of EPCs, the mechanisms of EPCs in treating CVDs, the potential diagnostic role of EPCs in predicting CVDs, as well as the main strategies for cardiovascular biomaterials to capture EPCs.

Keywords Cardiovascular biomaterials · Rapid endothelialization · Endothelial progenitor cells · Endothelial progenitor cell capturing stent · Predictive diagnostics · Targeted prevention · EPC-specific molecules · Predictive preventive personalized medicine (PPPM/3PM)

Abbreviations

CVDs Cardiovascular diseases
BMS Bare metal stents
DES drug-eluting stents
EPCs Endothelial progenitor cells
PPPM Predictive, preventive and personalized medicine

SMCs Smooth muscle cells
ISR In-stent restenosis
ECS Endothelial progenitor cell capturing stent
ECs Endothelial cells
CEPCs Circulating endothelial progenitor cells
NO Nitric oxide
eEPCs Early endothelial progenitor cells
lEPCs Late endothelial progenitor cells
OECs Outgrowth endothelial cells
KDR Kinase insert domain receptor
CXCR-1 Chemokine receptor 1
MMPs Matrix metalloproteinase
VEGF Vascular endothelial growth factor
cGMP Cyclic guanylate monophosphate
Dopa Dopamine
SeCA Selenocystamine
ECM Extracellular matrix
VEGF-R2 Vascular endothelial growth factor receptor 2

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PGI ₂	Prostaglandin I ₂
PAD	Peripheral arterial disease
CAD	Coronary artery disease
GM-CSF	Granulocyte-macrophage colony-stimulating factor
VE-cadherin ⁺	Vascular endothelial-cadherin ⁺
CFU-ECs	Endothelial cell colony-forming units
CECs	Circulating endothelial cells
IECs	Inflammatory endothelial cells
REDV	Arg-Glu-Asp-Val
PEG	Polyethylene glycol
vWF	Von Willebrand factor
SELEX	Systematic evolution of ligands by exponential enrichment
PPAam	Plasma polymerized allylamine
RGD	Arg-Gly-Asp
cRGD	Cyclic Arg-Gly-Asp
PCL	Polycaprolactone
PLLA	Poly (L-lactic acid)
ECFCs	Endothelial colony forming cells
TPS	TPSLEQRTVYAK
HCP-1	Hemocompatible peptide-1
EMF	External magnetic field
SPION	Superparamagnetic iron oxide nanoparticles
CA	Citric acid

Introduction

Cardiovascular diseases (CVDs), mainly caused by atherosclerosis and thrombosis, have become the leading mortalities in the past few decades [1, 2]. Cardiovascular stent intervention is proved to be an effective strategy to treat CVDs in clinical [3, 4]. However, a series of complications including inflammation, late thrombosis, and restenosis after long-term intervention limit the use of traditional cardiovascular stent [5, 6]. In order to overcome these limitations, drug-eluting stents (DES) have been systematically designed and investigated in recent years. The main principle of DES design is to inhibit the excessive proliferation of smooth muscle cells (SMCs) through cytotoxic drugs [7]. Although the DES lowers the incidence of in-stent restenosis (ISR) for short-periods, researchers have confirmed that the anti-proliferative drugs eluted on the DES could influence vascular healing process in a long term, which may increase the risk of late thrombosis [8–10]. It is well known that how to minimize the risk of ISR and accelerate the endothelialization process are the two most critical points in the success of cardiovascular stent. Based on the two principles, a novel vascular technique selectively recruits endothelial progenitor cells (EPCs) by the immobilized bioactive molecules, which is so-called endothelial progenitor cell capturing stent (ECS), has been developed

[11–13]. Although these novel vascular stents have shown great therapeutic effects in clinical, the subject has not been completely addressed till now, which reminds us to pay more attention to the most advanced cost-effective approach in biomedical sciences and healthcare [14]. The advanced concepts of PPPM (3 PM) has been presented by the European Association for Predictive, Preventive and Personalized Medicine (EPMA) as applicable to both “disease care” and “health care” [15]. The general report suggested that the number alteration of EPCs and some secondary complications especially inflammatory could serve as predictive judgments of potential CVDs, which provide a new strategy for the prevention and treatment of CVDs [16, 17].

In this review, we first introduce the biology of EPCs and mechanisms of EPCs in treating CVDs. More importantly, the potential role of EPCs as diagnostic biomarkers in predicting CVDs was also discussed in this review, contributing therefore to the prevention of CVDs as well as emphasizing the crucial role of EPCs in treatment of CVDs. On the other hand, we introduce the different approaches for EPCs capturing, including EPC-specific antibodies, aptamers, EPC-specific peptides, and magnetic molecules. The key factor of the subject is to maximize the number of captured EPCs through bioactive molecules. Therefore, it is essential to understand how to regulate the behaviors of EPCs and their responds toward corresponding molecules.

The definition and classification of EPCs

EPCs, the precursor of vascular endothelial cells mainly derived from bone marrow, have been firstly isolated by Asahara in 1997 [18–22]. Since then, the research on the biological characteristics and therapeutic effects of EPCs has become a new hot spot due to their potential in forming angiogenic and differentiating into functional endothelial cells (ECs) [23]. In fact, in addition to the bone marrow, umbilical cord blood, circulating blood, and arterial walls also contain EPCs but not more [24–27]. Zammaretti et al. confirmed that only about 0.01% of EPCs exist in human circulating blood [28]. Circulating EPCs (CEPCs) are mainly mobilized from non-hematopoietic tissues such as blood vessel walls and homed to the damaged endothelium and then form new layers [29–32]. The vascular endothelium, acting as a barrier between the blood and SMCs, plays a crucial role in maintaining the normal flow of blood [33, 34]. Not only can it prevent the formation of thrombus but also releases regulation mediators including nitric oxide (NO), soluble thrombomodulin, soluble E-selectin, prostacyclin, and tissue-plasminogen activators to keep vascular patency [35, 36]. More recently, a strong correlation has also been found between the status of endothelium and CVDs, which may serve as early indicators to predict cardiovascular disorders [37]. Such reliable indicators could

be classified into two main categories, including (a) cytokines mentioned above and (b) EPCs. Since EPCs possess huge potential in endothelium regeneration, predicting endothelial dysfunction and achieving rapid endothelialization through EPCs are of great significance for the treatment of CVDs [38]. Although the other approach for rapid endothelialization, which is so-called EC pre-seeding, also presented promising effects, the clinical trials showed a 3-week lag phase in preventing thrombus after implantation [39, 40]. In addition, the poor engraftment of host mural cells as well as low survival rate of ECs has also hampered its further development [41]. Therefore, researches on capturing circulating EPCs through cardiovascular biomaterials have been paid much attention.

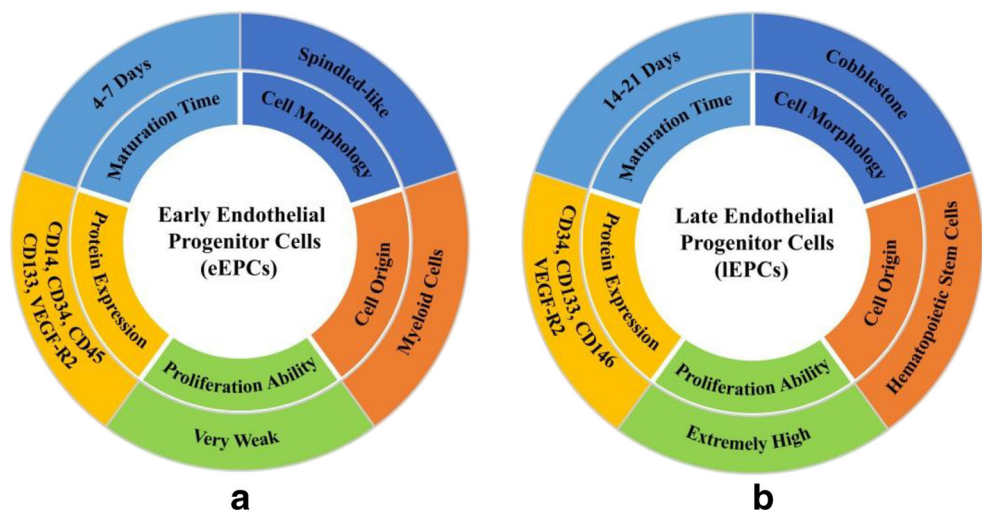
Depending upon the time of culture, EPCs can be classified into two types, which are called early EPCs (eEPCs) and late EPCs (lEPCs), respectively [42]. The reason for this division is based on their maturation time; eEPCs emerged after 4–7 days of culture while 14–21 days for lEPCs [43]. Although it is literally just a difference in culturing time, the distinctions of the two subpopulations are as follows (Fig. 1): (i) Cell origin—eEPCs, whose properties similar to CD14⁺ cells, are also defined them as CD14⁺ EPCs. Rehman et al. reported that the origin of these cells is myeloid or hematopoietic progenitor cells [44], whereas lEPCs, also named them as outgrowth endothelial cells (OECs) or CD34⁺ EPCs, are similar to the circulating bone marrow-derived from CD34⁺ hematopoietic stem cells [36]; (ii) Cell morphology—the eEPCs exhibit a spindled-like morphology while the lEPCs often express cobblestone morphology [45]; (iii) protein expression—it has already been proved that both of the subpopulations could express some identical surface makers, such as CD34, CD133, and vascular endothelial growth factor receptor 2 (VEGF-R2, also known as kinase insert domain receptor) [46, 47]. However, several other cells including dendritic cells and macrophages could also respond to VEGF-R2 while

CD34 could be expressed by megakaryocytes [21, 48, 49]. Therefore, the applications of utilizing these nonspecific factors to capture EPCs remain many limitations. In addition to the abovementioned factors, most cytokines, whatever types or amount, suffer great differences between the two. Yoon et al. demonstrated that eEPCs express CD14 and CD45 whereas lEPCs do not show the expression of the antigens [50]. Their previous research also reported that lEPCs showed a higher expression level of kinase insert domain receptor (KDR) and chemokine receptor 1 (CXCR-1) compared with eEPCs [51]. On the contrary, the expression of other surface markers by lEPCs, such as WAS and LYN which is related to hematopoiesis, is less than eEPCs [52]; and (iv) cell proliferation ability and differentiation ability—Zhang et al. reported that the proliferation ability of eEPCs is so weak that they can hardly be passaged. However, lEPCs possess extremely high proliferation potential and the capacity to form capillary-like tubes, which is similar to microvascular ECs [53, 54].

The mechanisms of EPCs in treating CVDs

It is generally accepted that EPCs could migrate from bone marrow into circulating blood and then home into the injured vascular sites when thrombosis occurs [55]. Shantsila et al. reported that circulating EPCs are responsible for postnatal neovascularization due to the high proliferation potential [56]. Accordingly, EPCs exert their effects based on the following two mechanisms: Firstly, during the formation of vascular networks, EPCs can incorporate into new vascular tissues directly. Secondly, EPCs also release several angiogenic mediators including vascular endothelial growth factor (VEGF), NO and matrix metalloproteinase (MMPs), etc., contributing to both endothelial repair as well as neointimal formation [57, 58]. Studies on these factors confirmed that they can accelerate the endothelialization process at some degree.

Fig. 1 **a** The characteristics of eEPCs and **b** the characteristics of lEPCs



For instance, VEGF, an important factor for angiogenesis, can not only promote EC migration and proliferation but also accelerates thrombosis resolution [59]. Li et al. immobilized VEGF on the MePBMTM coatings through covalent bonding [60]. After culturing for 3 days, a large number of EPCs with completely expanded state were observed on MePBMTM-VEGF sample. Besides, the platelets adhered on MePBMTM-VEGF sample not only remained a dendritic shape but also presented the lowest platelet adhesion level among all the groups. The experiments demonstrated that surface modification via VEGF could simultaneously address two issues: endothelialization and preventing thrombus formation. NO is also a crucial mediator in vascular endothelialization by supporting the behaviors of ECs migration and proliferation and EPCs differentiation. On the other hand, the adhesion of platelets and SMCs could also be inhibited by NO via upregulating cyclic guanylate monophosphate (cGMP) [61]. Yang et al. developed a one-step method to construct NO-generating coatings by dipping dopamine (Dopa) and selenocystamine (SeCA) in aqueous solution [62]. The results suggested that the SeCA-Dopa coatings could enhance the migration and proliferation of ECs while simultaneously inhibit these activities of SMCs due to the generation of NO gas. MMPs, an important mediator in thrombus formation, are increasingly valued thanks to their functions in capillary formation and neovascularization [63]. Kanayasu et al. discovered that MMPs could also stimulate ECs and EPCs through degrading extracellular matrix (ECM) components [64]. Therefore, mediator regulation is an extremely important mechanism for EPCs in treating CVDs.

What occurs when the vascular endothelium is injured? Initially, the neighboring mature ECs were thought to replace the injured vascular sites through migration and proliferation. However, only a small number of ECs were detected in the injured endothelium [65]. It seems to imply that there may be another repair mechanism (Fig. 2). Several studies related to the phenomenon were reported both in human and animal models. For example, in mice model, a sharp increase in the number of EPCs recruited by VEGF had been discovered by Kallka and his colleges [66]. Further studies also suggested that EPCs have the capability to form capillary-like tubes in ECM environment *in vitro* and thereby participating in constructing vascular networks [67]. Additionally, *in vivo* experiments reported that cells which could secrete VEGF-R2, such as immature CD133⁺ hematopoietic stem cells, maintained a high degree of coverage on the vascular implants, leading to the further recruitment of EPCs and re-endothelialization process [68]. Through a balloon injury model, EPCs were found to localize to neovascularization sites spontaneously. At the same time, the inhibition on SMCs activities and neointima formation were also detected [69]. The overall results not only indicated that

EPCs play an important role in re-endothelialization process but also open a new approach to treat CVDs.

In addition to the promotion effect in repairing vascular endothelium, it is well accepted that EPCs could also exert huge influence on thrombus propagation. Several studies in human experiments have confirmed this fact. Miglionico et al. reported a clinical trial consisted of 80 patients who received ECS surgery [70]. Sixteen months clinical observation showed that the average stenosis for these patients was $2.2 \pm 2.5\%$ and the minimal lumen diameter was 3.3 ± 0.5 mm, both significantly lower than preoperative. The experiments strongly demonstrated that the ECS, with almost no formation of thrombus propagation, could simultaneously achieve resist coagulation and promote endothelialization. Accordingly, Li et al. anticipated that the phenomenon may be attributed to the effect of antithrombogenic mediators, such as NO and prostaglandin I₂ (PGI₂) [71]. NO, as mentioned above, can not only increase ECs proliferation but also suppresses platelet adhesion and aggravation. PGI₂ is one of the most important substances secreted by EPCs, resulting in the inhibition on platelets and reduced risk of thrombus propagation [72].

The role of EPCs as potential diagnostic biomarkers in predicting CVDs

The number fluctuations of EPCs as predictive biomarkers of CVDs

Predictive diagnostics and targeted prevention, the two main aspects of PPPM, have been widely recognized by not only experts but also patients in recent years [73]. Encouraged by PPPM, the prevention of chronic symptoms related to CVDs has attracted much attention. Current data have demonstrated that several chronic conditions including peripheral arterial disease (PAD), coronary artery disease (CAD), and hypertension are strongly related to the number of EPCs [74, 75]. Therefore, the number fluctuation of EPCs could serve as an important diagnostic biomarker of these diseases, which is in great accordance with the concept of PPPM.

PAD, a serious complication caused by diabetes, threatens almost 20% elderly aged over 65 and it causes striking mortality rate [75]. Researchers have preliminary explored the relationships between number of EPCs and patients with PAD (Table 1). It was shown by Fadini that diabetes patients with PAD have decreased number of EPCs compared with those with diabetes alone [76]. Their further experiments also proofed the view that diabetes patients with PAD had lower expression levels of CD34, CD133, and KDR compared with diabetes free from PAD [77]. In order to determine the differences between subjects with and without PAD, Hayek et al. defined the CD34⁺/KDR⁺ counts as the number of EPCs [78]. The results showed that the EPCs counts in CAD patients with

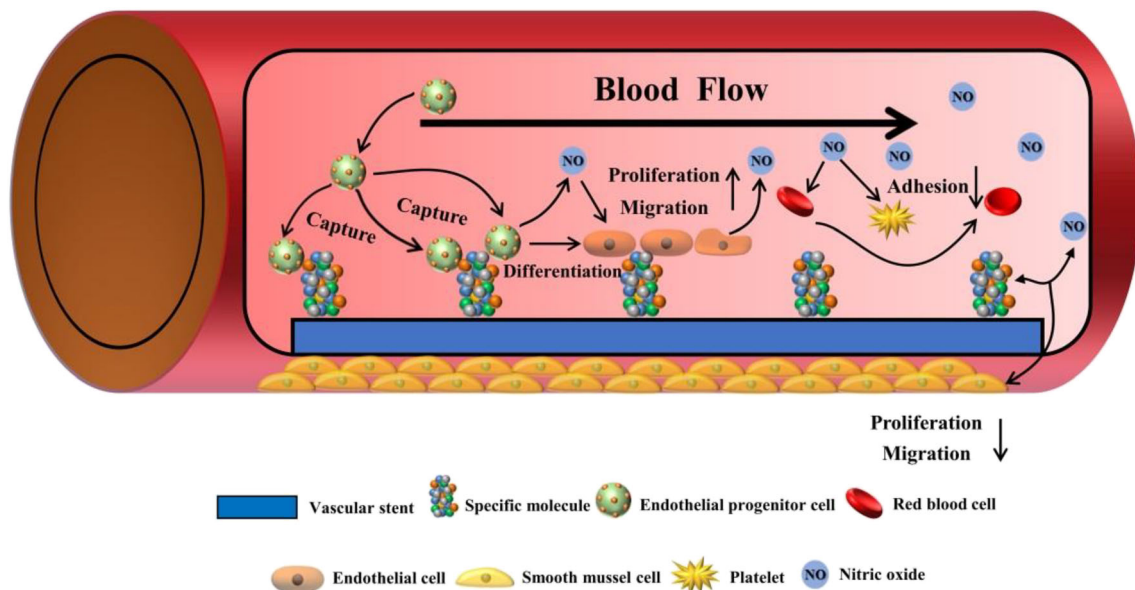


Fig. 2 The schematic diagram of vascular repair by capturing circulating EPCs. After being recognized by specific molecules on cardiovascular biomaterials, the EPCs can home into the damaged sites where they differentiate into endothelial cells, thereby accelerating the re-

endothelialization process. NO, released by the EPCs and mature ECs, could simultaneously inhibit the adhesion of platelets and SMCs, as well as promoting the growth of ECs

PAD symptom suffered a nearly 50% reduction compared with those with only CAD. Similar results were also reported by Bitterli et al. when compared with healthy subjects [79]. However, different measurement standards may cause completely different counting results. Morishita et al. and Delva et al. considered the amounts of $CD34^+/CD133^+/KDR^+$ cells as the number of EPCs and reported that PAD patients seem to have an increase in both number and function levels of EPCs [80, 81]. Besides, the varieties of proteins related to EPCs mobilization including pentraxin-3 and membrane type 1 matrix metalloproteinase (MT1-MMP) were also detected. Pentraxin-3, secreted by endothelial cells, could intuitively reflect inflammation conditions of endothelium, while the expression of MT1-MMP was highly related to vascular remodeling [75, 89, 90]. The results showed that the concentrations of pentraxin-3 were upregulated while MT1-MMP was downregulated in PAD patients when compared with healthy subjects. All in all, no matter which kinds of measurement standards, it is feasible to predict PAD according to the number of EPCs.

Increasing evidence has confirmed that the circulating EPCs are responsible for the endothelium repair after severely damaged, which means a reduction in EPCs counts may reflect whether a patient has CAD syndromes [91]. The number and function levels of EPCs have been reported to inversely correlate with risk factors for CVD-related symptoms such as age, smoking, and hypertension [92]. Vasa et al. revealed that smoking is the primary culprit for the reduction of EPCs, while the impaired levels of EPCs migration toward VEGF may be attributed to hypertension [82]. Taking 2-month

clinical results as an example, patients diagnosed with CVDs were more likely to be smokers with a high prevalence of older population [92]. These risk factors could barricade off signaling pathways of granulocyte-macrophage colony-stimulating factor (GM-CSF) and VEGF as well as those associated with cells differentiation and migration [75]. Despite the common risk factors, patients diagnosed with CAD also have individual factors such as family history. Another representative example is a study involving 45 patients with CAD syndromes; the results showed that those suffered from family history presented a slight reduction in EPCs migration, which supports family history as one of the individual factors. Therefore, the family history, as an important composition of “individualized patient profile,” could serve as an early indicator for CAD prediction [93]. With the applying of flow cytometry technique, the counts of circulating EPCs in human blood could be determined as $CD34^+/KDR^+$ cells. For this, Vasa et al. observed a 48% reduction in CAD patients compared with healthy subjects [82]. In addition to the number of $CD34^+/KDR^+$, Briguori et al. also evaluated the number of $CD34^+/vascular\ endothelial-cadherin^+$ (VE-cadherin⁺) as well as endothelial cell colony-forming units (CFU-ECs) with the purpose of clarifying the variety of EPCs levels during the CAD progression [83]. Specifically, both levels of $CD34^+/KDR^+$ and $CD34^+/VE-cadherin^+$ in CAD progressors were reduced by 37.5%, whereas those levels of CFU-ECs were also reduced by 28% compared with nonprogressors. More importantly, the author pointed out that the levels of CFU-ECs could predict CAD progression more precisely than $CD34^+/KDR^+$. Eizawa et al. also noted similar findings when

Table 1 A brief overview of several current studies on the relationships between EPCs and CVDs

Study	Subjects	Types of EPCs	EPCs number	EPCs function
Fadini et al. [76]	Diabetes patients with PAD Healthy	CD34 ⁺ /KDR ⁺	CD34 ⁺ /KDR ⁺ ↓	No data
Fadini et al. [77]	Diabetes patients with PAD Diabetes patients free from PAD	CD34 ⁺ /CD133 ⁺ /KDR ⁺	CD34 ⁺ /CD133 ⁺ /KDR ⁺ ↓ in diabetes patients with PAD	Clonogenic and adhesion ability ↓ compared with diabetes patients without PAD
Hayek et al. [78]	CAD patients with PAD CAD patients free from PAD	CD34 ⁺ /KDR ⁺	CD34 ⁺ /KDR ⁺ ↓ in CAD patients with PAD	No data
Bitterli et al. [79]	PAD patients Diabetes patients with PAD Healthy	CD34 ⁺ /KDR ⁺	CD34 ⁺ /KDR ⁺ ↓ in PAD patients	Proliferation ability ↓ in PAD patients
Morishita et al. [80]	PAD patients Healthy	CD34 ⁺ /CD133 ⁺ /KDR ⁺	CD34 ⁺ /CD133 ⁺ /KDR ⁺ ↑	pentraxin-3 ↑ and MT1-MMP ↓ in PAD patients
Delva et al. [81]	PAD patients Healthy	CD34 ⁺ , CD133 ⁺ , CD34 ⁺ /KDR ⁺ CFU-ECs	CFU-ECs ↑, CD34 ⁺ and CD133 ⁺ ↓	Proliferation ability ↑ in PAD patients
Vasa et al. [82]	CAD patients Healthy	CD34 ⁺ /KDR ⁺	CD34 ⁺ /KDR ⁺ ↓	Migratory ability ↓ in CAD patients
Briguori et al. [83]	CAD patients	CD34 ⁺ , CD133 ⁺ , CD34 ⁺ /KDR ⁺ , CD34 ⁺ /VE-cadherin ⁺ , CFU-ECs	CD34 ⁺ /KDR ⁺ , CD34 ⁺ /VE-cadherin ⁺ and CFU-ECs ↓ in CAD progressors	Proliferation and differentiation ability ↓ in CAD progressors
Eizawa et al. [84]	CAD patients Healthy	CD34 ⁺	CD34 ⁺ ↓	No data
Pirro et al. [85]	Essential hypertension (never treated) Essential hypertension (treated with Ramipril)	CD34 ⁺ /KDR ⁺	CD34 ⁺ /KDR ⁺ ↓ CD34 ⁺ /KDR ⁺ ↑	HOXA9 expression ↓ HOXA9 expression ↑
Oliveras et al. [86]	Hypertension patients	CD34 ⁺ /CD45 ⁺ /CD133 ⁺	CD34 ⁺ /CD45 ⁺ /CD133 ⁺ ↓	No data
Budzyń et al. [87]	Resistant hypertension patients Mild hypertension patients	CEPCs/CECs ratio	CEPCs/CECs ↓ CEPCs/CECs ↓	Triglycerides ↑ LDL-cholesterol and hsCRP ↑
Szpera-Goździewicz et al. [88]	Pregnant women with chronic hypertensive Healthy	CEPCs/CECs ratio	CEPCs/CECs ↓	vWf expression ↓

considered CD34⁺ cell populations as an indicator for the levels of EPCs [84]. In summary, reduced levels of EPCs including the cells of CD34⁺, CD34⁺/KDR⁺, CD34⁺/VE-cadherin⁺, and CFU-ECs may serve as indicators to predict potential patients with CAD.

Hypertension (particularly chronic hypertension), one of the major risk factors for cardiovascular, is emerged as the strongest indicator of EPCs migratory impairments [82]. By utilizing the above mentioned quantifying methods, although decreasing number of EPCs from hypertension patients were observed, we must acknowledge that these methods could not reflect the balance between regeneration and degradation of vascular endothelium [85, 86]. Therefore, a number of studies have focused on the ratio between CEPCs and circulating endothelial cells (CECs). The detachment of CECs from vascular walls could be attributed to various kinds of physiological mechanisms, such as apoptosis, mechanical damage, and

the lack of anchoring proteins [94]. The number of CECs is thereby considered to be a diagnostic biomarker for endothelial dysfunction. On the contrary, CEPCs are mainly originated from the bone marrow and tend to home into the damaged endothelium and then form new layers. Therefore, the number of CEPCs represents the capacity of endothelial regeneration at some degree. With this quantifying method, Budzyń et al. reported a significant lower CEPCs/CECs ratio in hypertension patients compared with healthy subjects, which indicated an insufficient process of endothelial regeneration in hypertension conditions [87, 95]. Moreover, it was shown that a CEPCs/CECs ratio below 2.72 highly indicated a potential risk of hypertension. Szpera-Goździewicz et al. compared the levels of CEPCs/CECs between the healthy control and the pregnant patients with different hypertension disorders. It seemed that patients with chronic hypertension tend to present the lowest number of CEPCs and the highest number of

CECs, leading to the lowest value of CEPCs/CECs among all the groups [88]. Although further studies are required to focus on the detailed mechanisms of EPCs in predicting hypertension, the accumulated data has already showed us a promising future of EPCs in predicting hypertension.

The inflammation related to EPCs as predictive biomarkers of CVDs

Recently, certain secondary complications especially inflammatory have been considered a link between macrophages and EPCs. That is because certain subpopulations of EPCs can be academically classified as immune cells [96]. For example, of the many known cells, circulatory angiogenic cells, eEPCs, and CFU-ECs are the representative derived from monocyte lineage, while angiogenic T cells are one of the subpopulations of CFU-ECs [96]. Previous studies have demonstrated that systemic inflammation could serve as an impetus for homing of EPCs, which plays an essential role in the regeneration of injured endothelium [97]. Under these circumstances, certain inflammatory responses were proposed as another predictive biomarker of CVDs. Holmen et al. noted that the inflammatory endothelium will lead to the detachment of inflammatory endothelial cells (IECs) from injury sites, and those cells may in turn contribute to persistent vascular damage by inducing the dysfunction of EPCs [98]. Besides, an inverse correlation should be noted between inflammatory cytokines (e.g., macrophage inflammatory protein-1 δ , E-Selectin, TNF- α) and EPCs levels in essential hypertension patients, suggesting the recruitment of EPCs in the process of endothelial regeneration may be inhibited by macrophages. The shift in macrophage phenotype from an inflammatory type to a common can be achieved through the interactions with EPCs, by which the inflammatory symptoms as well as the release of cytokines could be inhibited [99]. In addition to these general inflammatory responses, more emphasizes should be placed on the symptoms of individuals. Since personalized prevention is the most effective way to prevent cardiovascular disease. However, the role of EPCs in immune system is not well defined, which means further studies are required to provide a theoretical basis for personalized prevention.

The different approaches for cardiovascular biomaterials to capture EPCs

To improve the therapeutic effect of ECS, recent studies have paid much attention on surface modification via biomolecules. In order to achieve rapid endothelialization, EPC-specific antibodies, aptamers, peptides and magnetic molecules, and four main types of modified biomolecules have been widely utilized on cardiovascular biomaterials [100].

Applications of specific antibodies in EPCs capturing

Antibodies, a class of immunoglobulins that can specifically bind to antigens, are produced by human body due to the stimulation of antigen. Several types of antibodies such as anti-CD34, anti-CD133, and anti-CD146 have been applied to ECS due to their specific functions in cell recognition. Wu et al. immobilized heparin, Arg-Glu-Asp-Val (REDV) peptide, and anti-CD34 on Mg-Zn-Y-Nd surface which was alkali treated and silanized before, hoping to construct a multifunctional surface with superior blood compatibility and cytocompatibility [101]. The results indicated that the Hep/REDV/anti-CD34 coatings exhibited the biggest amount of NO release after 12-h culture, which markedly promoted ECs adhesion and proliferation. Besides, owing to the recognition ability of anti-CD34, the Hep/REDV/anti-CD34 coatings also presented much more EPCs attachment compared with other groups. Although the anti-CD34 modified surface had a good performance in capturing EPCs, convincing evidence found by Chen and co-workers has confirmed that the attachment of SMCs on anti-CD34 surface was no less than BMS, suggesting that the anti-CD34 surface was unable to prevent the adhesion and proliferation of SMCs [102]. An opposite case is that anti-CD34 was covalently prepared onto the polyethylene glycol (PEG) based Ti surface which was alkali heated and silanized in advance, improving the attachment of EPCs and inhibiting SMCs as well [103]. However, after cultivation for 3 and 5 days, the number of EPCs on the anti-CD34 coated surface is far less than the bare substrate. That means the coating may even prevent the proliferation of EPCs. Aiming to improve the capture efficiency of EPCs, Chen et al. also explored the influence of anti-CD34 orientation on biological effect [104]. Compared with the random immobilization, the oriented immobilized anti-CD34 not only had higher capture ability and efficiency but also expressed almost 3.48 times immunological binding activity. Unfortunately, the remained problem of SMCs attachment was still unresolved. Numerous clinical experiments have also demonstrated that anti-CD34 is defective to capture EPCs due to its nonspecific recognition [105]. For example, CD34 could also be expressed on hematopoietic stem cells, eEPCs and even on palates, which may lead to severe restenosis after surgery.

Based on this reason, researchers have focused on novel antibodies such as CD133, CD146, and anti-VE-cadherin. Duan et al. constructed a CD133/VEGF coating on a dopamine-hyaluronic acid/heparin-based layer [106]. Regardless of the static or stress conditions, the co-immobilized surface had the capability of re-endothelialization by enhancing the capture ratio of EPCs. In addition, with the cultivation time going on, the mRNA expression level of CD133 on co-immobilized surface suffered a great loss, while the mRNA of VEGF-R2, CD31, VE-

cadherin, and von Willebrand factor (vWF) expressed by ECs were significantly enhanced, indicating that the co-immobilized surface could support the differentiation from EPCs into ECs as well. Wawrzyńska et al. constructed a biocompatible surface via immobilizing anti-CD133 on a 316 L SS surface to control the cell behaviors [7]. The results showed that the anti-CD133 modified surface not only exhibited the strong promotion effect on EPCs adhesion but also dramatically reduced the risk of neointima hyperplasia and ISR by inhibiting the proliferation of SMCs. Although it is convinced that the anti-CD133-coated stent is better in capturing EPCs compared with anti-CD34, the number of cells that are sensitive to CD133 is too small, leading to the limited response to CD133. Recently, Park et al. prepared anti-CD146 combined with nanostructured SiNf on a CoCr stent, aiming at achieving rapid endothelialization and preventing neointima formation [107]. By using a porcine model, the modified stent presented an increased cell capture by approximately 8 times compared with the bare stent. The *in vivo* results also presented that the modified stent had the lowest neointimal ratio among all the groups. Both *in vitro* and *in vivo* experiments demonstrated that the co-existence of anti-CD146 and SiNf could target EPCs precisely and achieve rapid endothelialization. A similar case is that VE-cadherin was immobilized on PEG-coated stent, promoting endothelialization as well as preventing restenosis [108].

Applications of aptamers in EPCs capturing

Aptamers, a sequence of single-stranded RNA/DNA oligonucleotides with high affinity toward targets, are synthesized via a process named “systematic evolution of ligands by exponential enrichment” (SELEX) [109]. Aptamers were noticed due to their superior features including strong selective targeting abilities and super chemical stability. Even under biological conditions of extreme pH or temperature, they could still maintain more sensitive affinity than antibodies. Additionally, aptamers are more convenient to be synthesized and modified compared with antibodies [110]. Based on these superior features, plenty of studies are conceived to modify ECS by immobilizing aptamers.

With the help of SELEX technology, the ssDNA aptamers with high affinity to EPCs were prepared on star-PEG coatings by Hoffmann [111]. By using a porcine model, they demonstrated that the EPCs which were recognized by aptamers could differentiate into ECs within 10 days. Dopamine, well known for its mussel inspired functions, has been widely applied to construct a rich in amine surface [112]. Qi et al. used plasma polymerized allylamine (PPAam) platforms to absorb DNA aptamers through electrostatic interaction [113]. After co-culturing for several hours, the ratio of EPCs/SMCs on PPAam-DNA surface was nearly 2 times than that of the PPAam and 316 L SS. Similar results were also

observed in the case of EPCs/ECs. The ratio of PPAam-DNA increased by about 150% compared with the PPAam and 316 L SS, and no significant difference was found between the control groups, indicating that the modified surface had extremely high affinity in capturing EPCs under static conditions. To further investigate the EPCs-capture ability under dynamic conditions, Li et al. and Deng et al. immobilized DNA aptamers onto a dopamine-coated surface and then placed them in a flow chamber [114, 115]. After 4 h, both of their samples modified with DNA aptamers captured the largest number of EPCs among all the groups. These results suggested that the aptamers have great potential as bioactive molecules in realizing rapid endothelialization. However, aptamers are not always specificity in cell interaction. There is evidence that the capture ability may be affected by the affinity range. Yoon et al. prepared three clones of CD31 aptamer at a concentration of micro-meters range on EPCs and 293FT cells, aiming to test the feasibility of CD31 aptamer in visualizing EPCs [116]. But the nonspecific recognition was detected on both surfaces, which suggested that the appropriate affinity range plays an important role in specific interaction. Unfortunately, this field has not been valued in most studies. Under these circumstances, continued exploration in aptamers specificity, as an important point to improve the therapeutic effect of CVDs, was required to be done in further studies.

Applications of specific peptides in EPCs capturing

ECM, a friendly microenvironment for EPCs, plays an important role in promoting cell interaction, differentiation, and proliferation [117]. In addition to the above functions in cell behaviors, the ECM provides biochemical and mechanical supports for cells as well [118]. Typically, ECM is mainly composed of proteins and small bioactive molecules. As a consequence, remodeling a functional surface with ECM-derived proteins and small peptides is an ideal strategy to achieve rapid endothelialization. However, surface modification with proteins may cause a series of implications including proteolytic decomposition and conformational changes [119]. On the contrary, such serious implications can be minimized by the peptides due to the more stable structure [120]. Thus, it is widely accepted that peptides modification could realize better cell interaction in comparison with proteins.

The tripeptide sequence Arg-Gly-Asp (RGD), which can be specifically recognized by cell mediators such as $\alpha v \beta 3$ and $\alpha 5 \beta 1$, has been widely applied to improve the recruitment of EPCs. In order to evaluate the effects of a cyclic Arg-Gly-Asp peptide (cRGD) in recruiting EPCs, Blindt et al. used a newly polymer coating to load cRGD onto the stainless steel [121]. The dynamic capture experiments showed that the cRGD-modified stents captured a great number of EPCs while much fewer for bovine serum albumin-coated stents. Although the

cRGD at a concentration of 100 $\mu\text{g/ml}$ resulted in an increase in attached cell number compared with 1 $\mu\text{g/ml}$, the gap between the two was almost negligible. Similar tendency was also observed in the EPC- and SMC-specific recognition experiments. It means that they had not determined an appropriate amount of cRGD loaded on the stents. Further research by Le Saux et al. confirmed that RGD at a density of 0.1 fmol/cm^2 is the lowest density to promote ECs adhesion and that 10 fmol/cm^2 is required for the cells spreading on the RGD modified surface [122]. Based on this theory, Royer et al. immobilized GRGDS at a density of $1.9 \pm 0.1 \text{ pmol/mm}^2$ to fabricate a polyethylene terephthalate (PET) micro-patterned surface in which sitagliptin was combined [123]. Regardless of the different sizes of patterns, the GRGDS/Sita surface largely reduced the number of CD 34 positive cells by about 50%, indicating that the combination of the two peptides could induce the differentiation of EPCs into ECs. However, due to the general adhesive property of GRGD peptide, it is impossible to avoid nonspecific interactions between GRGD and other cells or proteins [124].

In order to solve this problem, Hao et al. then developed a novel cyclic peptide named LXW7 which mainly achieves specific recognition to EPCs/ECs via $\alpha\text{v}\beta\text{3}$ integrin [125]. Contrary to the typical cRGD peptide, LXW7 possesses highly binding selectively to EPCs/ECs, low affinity to platelets, as well as no affinity to monocytes, which can be attributed to its stable cyclic structure. To further evaluate the guidance of LXW7 on EPCs, Hao et al. immobilized LXW7 on polycaprolactone/poly (L-lactic acid) (PCL/PLLA) surface through a click chemistry method [126]. The results showed that endothelial colony forming cells (ECFCs), a subpopulation of EPCs, were specifically captured from circulating blood by the modified surface. While at the same time, a mouse model also demonstrated that the modified surface was able to minimize thrombus formation and thereby maintaining vascular patency, which indicated an excellent ability in promoting re-endothelialization.

TPS is another EPC-specific peptide and has been used as an aptamer for recruiting EPCs in the past few years. Chen et al. used a two-step condensation reaction to prepare dopamine and TPS peptide onto a titanium (Ti) surface [127]. The modified surface not only showed obvious inhibition effects on platelets attachment but also supported the adhesion and proliferation of EPCs. Through a CCK-8 assay and in vivo experiments, similar results were also observed on a TPS and bovine serum albumin co-immobilized Ti surface [128]. It seems that the incorporation of TPS peptide and bioactive molecules could construct a suitable microenvironment for EPCs. In addition, other EPC-adhesive peptides, such as hemocompatible peptide-1 (HCP-1) and YIGSR, have also been proved to exert an outstanding effect on recruiting EPCs [40, 129].

Applications of magnetic molecules in EPCs capturing

Magnetic molecules, which are effective in tracking and capturing EPCs, act through an external magnetic field (EMF) to localize EPCs to the injured vessels [130]. Based on this theory, superparamagnetic iron oxide nanoparticles (SPION) have been widely applied in surface modification. Wilhelm et al. reported that the biological behaviors of EPCs could be influenced by particle sizes as well as the concentrations of SPION [131]. Since then, a series of exploration have been reported on the impacts of the above two factors on tracking EPCs. Carezza et al. reported that the capture efficiency for the large aggregated nanoparticles was seven times higher compared with those of the dispersed group, with almost equivalent cell viabilities and functions [132]. As for the best choice for the SPION concentration, it was initially assumed that the concentrations ranged within 0–50 $\mu\text{g/ml}$ were safe for biological activities of EPCs [133, 134]. Later, with no significant weaken in proliferation potential and cell viabilities between labeled and unlabeled EPCs, the safe concentration was extended to 70 $\mu\text{g/ml}$ by Wei and co-workers [135]. However, several studies also obtained satisfactory results at a concentration of 100 $\mu\text{g/ml}$, which seem to imply that the safest concentration of SPION for EPCs tracking remains unclear.

In addition, researchers have paid more attention to the development of new SPION materials. Zhang et al. successfully prepared a 10-nm thick single silica layer to wrap around a SPION core [136], while the silica-coated SPION in rat models significantly increased the aggregations of EPCs around the infarcted area where an EMF was applied, accompanied by an obviously enhanced density of capillaries and reduced area of infraction. More importantly, it seems to be the first report that an applied EMF can significantly facilitate the retention of EPCs in the ischemic myocardium. Recently, a novel method combined the SPION with specific antibodies was confirmed to have high affinity towards EPCs. Aiming at attracting EPCs to the injury sites via EMF to achieve re-endothelialization, Chen et al. modified Fe_3O_4 stent with anti-CD34 and citric acid (CA) [137]. As expected, compared with the group modified with single anti-CD34 or CA, the incorporation of the two significantly increased the affinity of EPCs toward iron stent, indicating the excellent ability of SPION in attracting EPCs. To further detect the effects of EMF on dynamic EPCs capturing, the iron samples were placed in a flow chamber at a flow rate of 1 m/s. Three hours later, only a few cells were observed on the iron sample with no application of EMF. On the contrary, the stent under a 300-mT EMF was almost completely covered by EPCs. Therefore, this approach showed no inhibition effects on EPCs and possessed ability to guide the EPCs to the desired region and thereby achieve re-endothelialization.

Conclusions and expert recommendations

Depending upon the high proliferation potential, repairing the damaged endothelium by EPCs has been confirmed as a promising approach to accelerate re-endothelialization. There is no doubt that a better comprehension in EPCs biology could direct the modification strategies for cardiovascular biomaterials, but more importantly, it also plays a key role in the prevention and treatment of CVDs. Besides, applying the number fluctuations of EPCs in our bodies not only provide us early diagnostics and personalized prevention strategies but also practice the most advanced cost-effective approach in biomedical sciences and healthcare. Personalized prevention will definitely become an important strategy for the prevention and treatment of CVDs in the future. These tasks should be developed based on the number and function levels of EPCs in individualized patient. However, we must admit the current limitations associated to the methods in EPCs quantification. First, almost all the studies have a common limitation; that is, the number of subjects involved was too small. This factor may cause the experimental results to be non-universal. Secondly, it is widely accepted that the standardized criteria for isolating and quantifying EPCs are lacking, leading to the undesired alterations in functions of EPCs and thereby affecting experimental results in varying degrees. Therefore, we implicate that the standardized criteria as a significant yet underestimated factor for EPCs quantification should be noted in further studies.

The present review mainly focused on the basic introduction of EPCs, the mechanisms of EPCs in treating CVDs, and the potential diagnostic role of EPCs in predicting CVDs as well as capturing EPCs with some specific molecules including EPC-specific antibodies, aptamers, peptides, and magnetic molecules. Although numerous results showed that the re-endothelialization process can be accelerated at some degree, the affinity of these modified biomaterials toward EPCs still needs to be improved to meet the clinical requirement. Thus, how to enhance the combination efficiency between biomaterials and EPCs remains the main subject for further studies.

In order to address the unresolved issue, the following perspectives for future research may deserve more attention:

1. Shear stress to enhance the adhesion between EPCs and cardiovascular biomaterials. Accumulating evidence has proved that the adhesion of EPCs to a surface could be enhanced by pretreating with unidirectional laminar shear stress, but more importantly, the preimplantation adhesion of EPCs also largely promotes the regenerative potential of EPCs, including the capability of homing injuries, forming capillary-like tubes, as well as differentiation into mature ECs and thereby accelerating the process of endothelialization. Unfortunately, the perspective was hardly

considered in many current studies and deserves more attention in future research.

2. Modifications to minimize the adhesion of plasma proteins. EPCs are captured by the biomaterials through interactions with the bioactive sites provided by the specific molecules. However, the redundant plasma proteins such as fibrinogen may take the lead in binding with the bioactive sites, subsequently weakening the affinity of biomaterials toward EPCs. Therefore, both the amounts of absorbed plasma proteins and capture efficiency of EPCs should be considered in future research.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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