



# Regulation of Endothelial Progenitor Cell Functions in Ischemic Heart Disease: New Therapeutic Targets for Cardiac Remodeling and Repair

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Ischemic heart disease (IHD) is the leading cause of morbidity and mortality worldwide. Ischemia and hypoxia following myocardial infarction (MI) cause subsequent cardiomyocyte (CM) loss, cardiac remodeling, and heart failure. Endothelial progenitor cells (EPCs) are involved in vasculogenesis, angiogenesis and paracrine effects and thus have important clinical value in alternative processes for repairing damaged hearts. In fact, this study showed that the endogenous repair of EPCs may not be limited to a single cell type. EPC interactions with cardiac cell populations and mesenchymal stem cells (MSCs) in ischemic heart disease can attenuate cardiac inflammation and oxidative stress in a microenvironment, regulate cell survival and apoptosis, nourish CMs, enhance mature neovascularization, alleviate adverse ventricular remodeling after infarction and enhance ventricular function. In this review, we introduce the definition and discuss the origin and biological characteristics of EPCs and summarize the mechanisms of EPC recruitment in ischemic heart disease. We focus on the crosstalk between EPCs and endothelial cells (ECs), smooth muscle cells (SMCs), CMs, cardiac fibroblasts (CFs), cardiac progenitor cells (CPCs), and MSCs during cardiac remodeling and repair. Finally, we discuss the translation of EPC therapy to the clinic and treatment strategies.

**Keywords:** ischemic heart disease, endothelial progenitor cells, cardiac remodeling, cardiac repair, angiogenesis, crosstalk

## INTRODUCTION

Cardiovascular disease (CVD), primarily ischemic heart disease (IHD), remains the leading cause of global disability and mortality (1). IHD is characterized by a loss of myocardial cell function due to insufficient blood supply flowing from the coronary arteries to the heart, followed by ventricular dysfunction and progressive heart failure. After myocardial infarction (MI), tissue damage and necrosis initiate a series of pathological responses, such as inflammation, oxidative stress, neurohormonal system activation, and hemodynamic load regulation, which lead to fibrotic scarring during the replacement of lost cardiomyocytes (CMs) (2, 3). Subsequently, the injured heart undergoes remodeling which leads to further cardiac hypertrophy, ventricular dilation and reduced contractility involving cellular and interstitial changes at the myocardial tissue level, mainly fibrosis, which ultimately leads to fatal heart failure (4). The current treatment for IHD mainly involves percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) to achieve revascularization, increase blood supply and save the injured ischemic myocardium (5).

Stem cell therapy has been widely used to treat IHD, providing patients with drug-free and non-surgical treatment and encouraging safer and more feasible cardiac repair strategies (6). Endothelial progenitor cells (EPCs), also known as vascular endothelial precursor cells, exhibit the potential to enter the blood circulation and undergo proliferation and differentiation into multiple cell types (7). Studies have shown that EPC number and function are closely related to endothelial cell (EC) injury and dysfunction and can be used in the clinic as biomarkers of vascular function and cumulative cardiovascular risk (8). EPCs are involved in cardiac repair after MI through regulation of immune responses, neovascularization, extracellular matrix deposition and cardiac microenvironment formation. In this review, we introduce the biological characteristics and recruitment mechanism of EPCs, discuss the impact of crosstalk between EPCs and related cardiac cells and mesenchymal stem cells (MSCs) on cardiac remodeling and repair after ischemic cardiomyopathy, and report the current clinical implications of EPC therapy.

## THE DEFINITION, ORIGIN, AND BIOLOGICAL SIGNIFICANCE OF EPCs

In 1997, Asahara and colleagues were the first researchers to identify a population of cells capable of differentiating into mature ECs and undergoing postnatal angiogenesis, and they called the cells in this subset “putative endothelial progenitor cells” (9). It was initially thought that EPCs originated and resided in bone marrow (BM) and were mobilized to circulate in adult peripheral blood (PB) or umbilical cord blood (UCB) (10). Since no uniform isolation or culturing protocol for EPCs has been reported and because EPCs express different surface antigens at different stages of maturation or differentiation, EPC subpopulations exhibit various phenotypes (11). Two clear types of EPC have been identified on the basis phenotype and function: hematopoietic EPCs (myeloid) and endothelial lineage EPCs (12). The hematopoietic EPC lineage includes myeloid angiogenic cells (MACs), circulating angiogenic cells (CACs) and early EPCs. EPCs with this immunophenotype express CD45, CD14, and CD31 but not CD146 or CD133. These cells do not have the capacity to differentiate into ECs but promote angiogenesis through paracrine signaling. The endothelial lineage includes endothelial outgrowth cells (OECs) or late EPCs and endothelial colony-forming cells (ECFCs), which are also widely recognized as “bona fide EPCs” and show the ability to undergo clonal expansion and self-renewal, form blood vessels and intima, and continuously be incorporate into and contribute to the formation of the host vascular system (12–14). Recently, CD133, CD34, and VEGFR-2 (also known as KDR or Flk-1) have been the most commonly used biomarkers to identify or characterize EPCs (15). However, other recent studies have shown that circulating CD19<sup>-</sup> CD34<sup>+</sup> EPCs do not express VEGFR-2, which is expressed only in CD19<sup>+</sup> B cells (16). When expression of sca1<sup>+</sup>/flk1<sup>+</sup> cells were observed in mice, the expression of B-cell-specific surface markers was found to be upregulated. It has been speculated that currently

characterized EPCs are not truly EPCs but are lymphocytes, mainly B2 lymphocytes; therefore, scientists need to engage in further research and discussion (17). Although BM is considered the classic source of EPCs, Fujisawa et al. found that circulating EPCs isolated from vessel walls and PB of male patients who had undergone BM transplantation from female donors displayed XY genotype (18). In addition, Ingram et al. found that a complete hierarchy of EPCs can be identified in human umbilical vein ECs or human aortic ECs, showing that EPCs may originate from blood vessels (19). EPCs have been found to reside in the vasculature beds of various tissues, and CD157 or EPCR have been proposed as markers to identify tissue-resident EPCs (20). Surprisingly, a recent study reported marker genes, secreted factors, microRNAs (miRNAs), and growth factors of EPCs on the basis of single-cell transcriptomic analyses to better optimize and characterize the EPC subpopulation in adult PB. In this study, BMB2, BMP4, and Ephrin B2 were highly expressed only in EPCs, not ECs, in three different tissues. The neuropilin-1, VEGF-C, Notch 1, PECAM-1, and MIR-21 genes were differentially expressed. CD62L and PLAUR expression levels can be used as markers for the isolation and characterization of EPCs derived from monocytes (21).

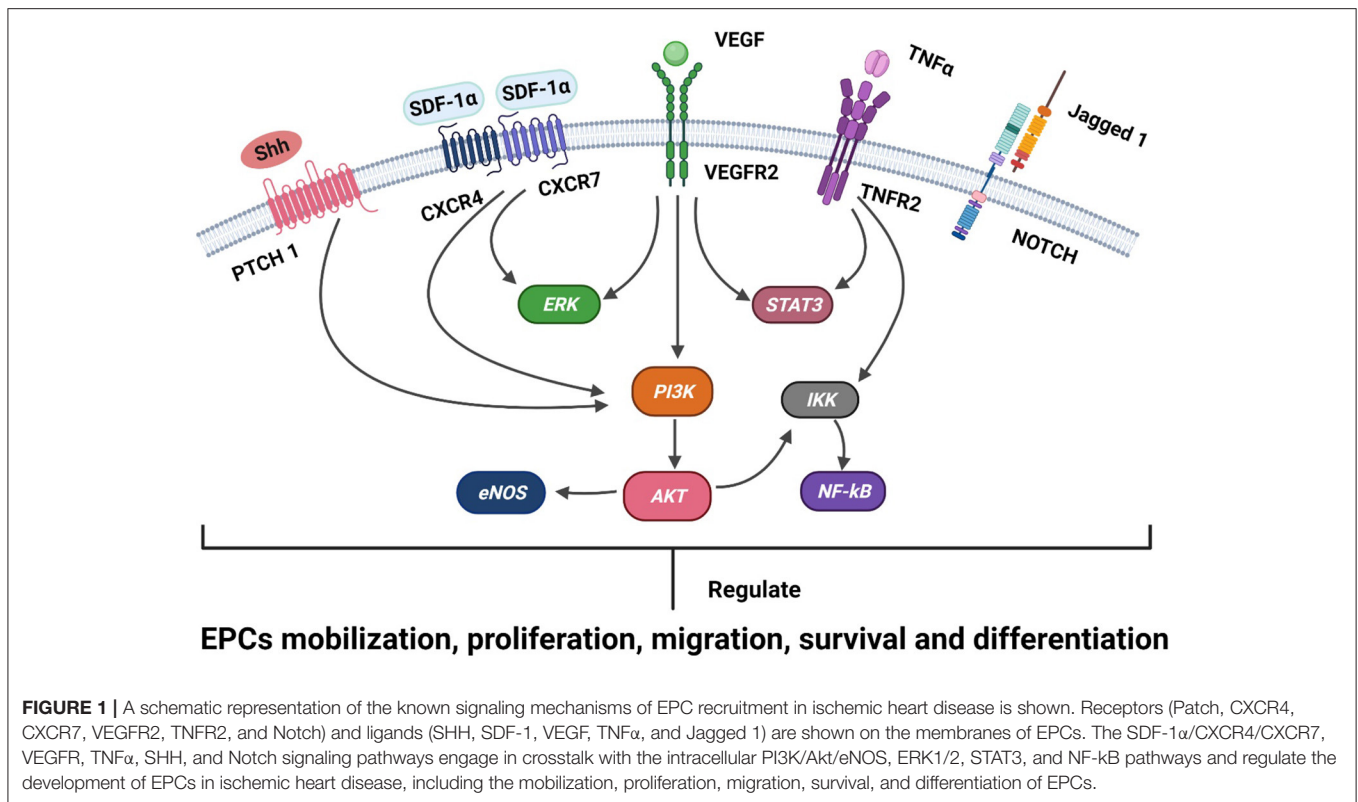
EPCs participate in vascular and cardiac repair in coronary atherosclerosis (22), ischemic cardiomyopathy (23), and diabetic cardiomyopathy (24). During tissue or vascular injury, circulating EPCs are recruited to injury sites, enabling the growth of new blood vessels that are formed from an extension of existing ECs (angiogenesis) or *de novo* (vasculogenesis) (25). At the same time, soluble factors and EPC exosomes (EXs) and microvesicles (MVs) secreted by EPCs can attenuate a deleterious microenvironment formed during inflammation and oxidative stress (26), regulate cell survival and apoptosis (27), inhibit mesenchymal cell transformation and fibrosis (28), promote the homing of stem/progenitor cells (29), nourish CMs and induce angiogenesis (30), thereby exerting beneficial effects.

## RECRUITMENT MECHANISM OF EPCs IN ISCHEMIC HEART DISEASE

EPCs are recruited from BM to ischemic tissues, and the processes (mobilization, proliferation, migration, and differentiation) that mediate neovascularization and re-endothelialization involve the regulation of multiple cytokines, receptors, adhesion molecules, proteases, and cell signaling mechanisms (31, 32) (Figure 1).

## EPC RECRUITMENT IS REGULATED BY NON-CODING RNAs

Non-coding RNAs (ncRNAs) constitute classes of genetic, epigenetic and translational regulators, including miRNAs, long ncRNAs (lncRNAs), and circular RNAs (circRNAs), which play important roles in the development of CVD (33). ncRNAs were also found to be involved in the biological activities of endothelial progenitor cells (EPCs), including their



mobilization, proliferation, migration, invasion, angiogenesis, and differentiation (Table 1).

MiRNAs are endogenous small non-coding single-stranded RNAs with regulatory activity that lead to degradation of target mRNA or reduced protein translation by binding to the complete or incomplete complementary site of the 3'-untranslated region (UTR) of target mRNA (49). Chang et al. identified the expression profiles of miRNAs in early EPCs, late EPCs, and human umbilical vein ECs, and this profile can be used to determine novel biomarkers for the prevention and treatment of coronary artery disease (CAD) (50). Previous reviews have presented summaries of the roles played by miRNAs in regulating EPC proliferation, mobilization, migration, differentiation, apoptosis, autophagy, senescence, adhesion, and tubule formation, as well as EPC-induced angiogenesis (51). EPCs face the challenge of hypoxia in ischemic tissue, and overexpression of miR-130a and miR-210-3p at the cellular level can enhance the proliferation, migration and tube formation of EPCs under hypoxic conditions (34, 35). Li et al. found that EPCs transfected with miR-326-5p exhibited significantly increased tube formation in Matrigel plugs and angiogenesis in the MI model (36). Liu et al. observed that miR-144-3p in circulating exosomes disrupted the MMP-9 pathway by targeting the expression of Ets1 in MSCs and inhibited the mobilization of EPCs after myocardial infarction (40). Notably, recent studies have revealed that overexpression of miR-324-5p and miR-126 in EPCs can reduce the apoptosis and reactive oxygen species (ROS) production rates and prevent oxidative stress-induced EPC damage (38, 39). Maintaining

the cardiac microenvironment by regulating oxidative stress can maintain endothelial stability and promote angiogenesis and remodeling.

lncRNAs are longer than 200 bp and exhibit regulatory ability but lack protein-coding capacity, and they play important roles in physiology and disease pathology (52). Li et al. found that the lncRNA WTAPP1 positively regulated the migration, invasion and angiogenesis of human peripheral blood-derived EPCs and mediated the effects of EPCs through the PI3K/Akt and autophagy pathways (41). By knocking down lncRNA-p21 expression, the adhesion and migration of EPCs were weakened, and the repairing effect of EPCs after vascular endothelial injury was disrupted (42). Overexpression of the lncRNA TUG1 promoted the migration and differentiation of EPCs and participated in angiogenesis (43, 44). The lncRNA MALAT1 inhibited EPC autophagy and apoptosis and increased cell viability by activating the mTOR signaling pathway, thereby delaying CAD progression (22). Xiao et al. found that lncRNA THRIL expression was upregulated in coronary atherosclerotic heart disease, and the lncRNA THRIL inhibited EPC proliferation and mediated autophagy through the AKT pathway and FUS protein activation (45).

circRNAs are non-coding RNAs in which the upstream 3' end is linked to the downstream 5' ends to form a closed-loop structure (53). circRNAs can regulate gene expression by regulating transcription and alternative splicing, interacting with RNA-binding proteins, or acting as miRNA sponges (54). Three studies revealed that mmu\_circ\_0000250 (46),

**TABLE 1** | Non-coding RNAs regulate EPCs recruitment.

Non-coding RNA	Positive/Negative	Targets	Function	Reference
<b>MicroRNA</b>				
miR-130a	+	VEGFR2/STAT3/HIF1 $\alpha$	Promotes EPCs proliferation, migration and tube formation under hypoxia	(34)
miR-210-3p	+	RGMA	Promotes EPCs proliferation, migration and tube formation under oxygen-glucose deprivation	(35)
miR-326-5p	+	Wnt1	Promotes angiogenesis ability of EPCs <i>in vitro</i> and <i>in vivo</i>	(36)
miR-126	+	Notch 1	Promotes EPCs proliferation, migration and invasion	(37)
	+	PI3K/Akt/GSK3 $\beta$ and ERK1/2	Promotes EPCs proliferation, migration and tube formation under oxidative stress	(38)
miR-324-5p	+	Mtfr1	Promotes the survival and proliferation of EPCs under oxidative stress	(39)
miR-144-3p	-	Ets1/MMP9	Impairs mobilization of EPCs	(40)
<b>lncRNA</b>				
LncRNA WTAPP1	+	miR-3120-5P/PI3K/Akt/mTOR	Promotes migration, invasion, and tube-forming ability of EPCs <i>in vitro</i> and <i>in vivo</i>	(41)
LncRNA-p21	+	SES2/AMPK/TSC	Promotes adhesion and migration of EPCs alleviates AngII-induced senescence	(42)
TUG1	+	miR-6321/ ATF2	Promotes EPCs migration, invasion and differentiation	(43)
	+	miR-29c-3p/PDGF-BB/Wnt	Promotes high glucose-impaired EPCs migration, invasion and tube formation	(44)
MALAT1	-	miR-15b-5p/MAPK1 and mTOR	Inhibits EPCs proliferation and autophagy	(22)
THRIL	-	AKT pathway and FUS protein	Inhibits the proliferation of EPCs	(45)
<b>circ RNA</b>				
mmu_circ_0000250	+	miR-128-3p/SIRT1	Promotes high glucose-induced EPCs survival and angiogenesis	(46)
hsa_circ_0058092	+	miR-217/FOXO3	Promotes high glucose-induced EPCs survival, proliferation, migration and angiogenic differentiation	(47)
circ-ADAM9	-	mir-20a-5p/PTEN and ATG7	Inhibits high glucose-induced EPCs survival and angiogenic differentiation	(48)

and hsa\_circ\_0058092 (47) circ-ADAM9 (48) targeted their corresponding miRNAs, regulated autophagy and apoptosis of EPCs after treatment with high concentrations of glucose, and protected the migration and angiogenesis capacities of these EPCs. Hence, circRNAs have been suggested to interfere with EPC biological functions by absorbing miRNAs. However, studies on circRNA-mediated regulation of EPC functions in IHD have not been reported, and further exploration is needed.

## EPC RECRUITMENT-RELATED SIGNALING PATHWAYS

### The SDF-1 $\alpha$ /CXCR4/CXCR7 Signaling Pathway

Stromal cell-derived factor-1 $\alpha$  (SDF-1 $\alpha$ ) expression is increased in MI areas, while SDF-1 $\alpha$  is required to stimulate stem/progenitor cell migration and homing to ischemic sites (55). Upon ligation with one of two receptors of the ligand SDF-1 $\alpha$  (also known as CXCL12), CXCR4 and CXCR7, SDF-1 $\alpha$  regulates the adhesion, transendothelial migration, proliferation, and tube formation of EPCs; specifically, EPC

chemotaxis is mediated through only CXCR4, while EPC survival is mediated through the interaction of SDF-1 $\alpha$  with CXCR7 but not that with CXCR4 (56). The CXCR7 expression levels were downregulated simultaneously in mouse myocardial tissue and EPCs after acute MI (AMI), and CXCR7 overexpression was found to rescue EPC migratory and angiogenic capacities (57). Qiu et al. found that SDF-1 $\alpha$  expression upregulation and coupling of SDF-1 $\alpha$  to the receptor CXCR4 contributed to anti-inflammatory and antiapoptotic effects after AMI (58). In addition, Fan et al. found that IL-1 $\beta$  promoted the EPC formation of capillaries and tubes in a CXCR7-dependent manner under inflammatory conditions and antagonized CXCR7 inhibition of EPC angiogenesis (59). The SDF-1 $\alpha$ /CXCR4/CXCR7 pathway activates multiple signaling pathways and regulates multiple biological processes in EPCs. For example, the PI3K/Akt/ nitric oxide synthase (eNOS) pathway played a key role in stem/progenitor cell recruitment and angiogenesis, and SDF-1 $\alpha$ -treated EPCs exhibited increased Akt and eNOS phosphorylation and nitric oxide (NO) production. However, PI3K inhibitor-induced Akt phosphorylation and eNOS expression were observed; thus, PI3K/Akt/eNOS pathway-mediated EPC apoptosis was inhibited (60–63). ERK participates

in molecular signaling pathways involved in cell survival, differentiation and proliferation, and the ERK signaling pathway is involved in CXCR4- or CXCR7-mediated EPC proliferation, migration and angiogenesis (64, 65).

## The Vascular Endothelial Growth Factor Receptor Signaling Pathway

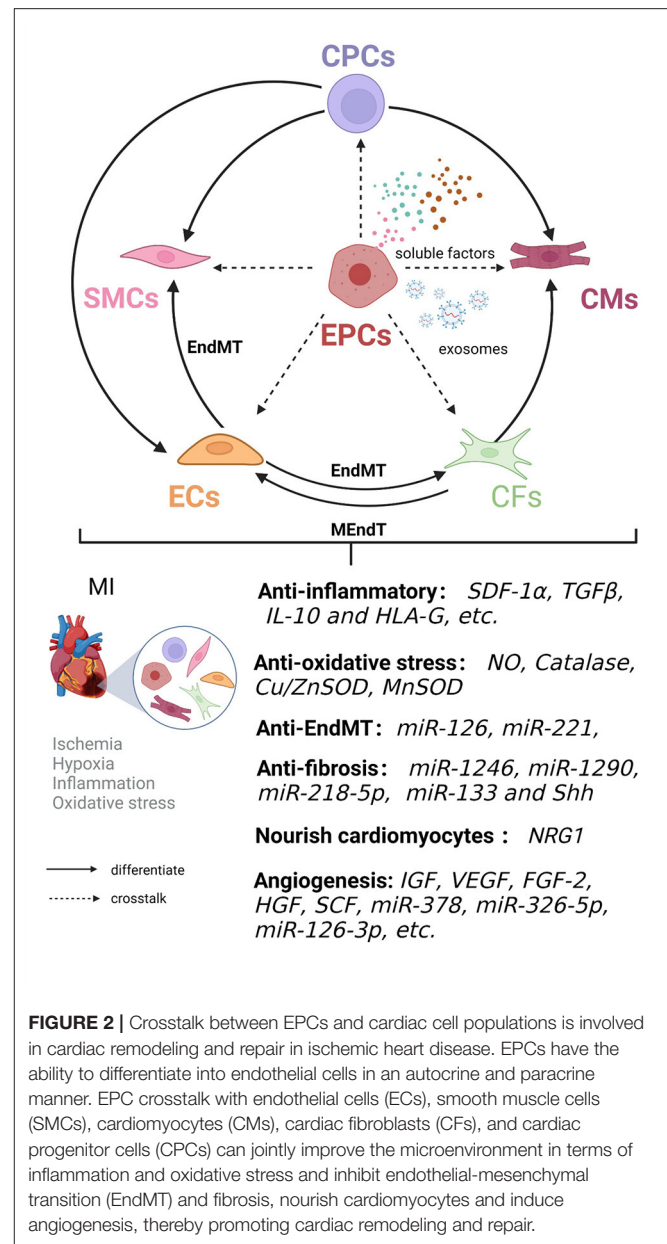
The mobilization, recruitment, and differentiation of EPCs and ECs are regulated by VEGF (66). VEGF increases the number of circulating EPCs and regulates *in situ* differentiation of EPCs and EPC formation of capillary plexuses (67). Hoffmann et al. used through high-throughput signaling pathway identification technology to examine the effect of VEGF signaling on BM-EPCs in the vasculature under hypoxia and found that VEGF-A-mediated VEGFR signaling was increased during hypoxia, while VEGF-A expression and VEGFR1 and VEGFR2 protein pathway activation was significantly increased (68). Interestingly, VEGF-A pathway activation in EPCs during hypoxia, while increases in related proteins were detected from NOS pathway, inositol and calcium signaling, G protein signaling, inflammation, and phospholipase signaling (68). In addition, VEGF has been shown to bind to VEGFR2 and activate the PI3K/Akt/eNOS (69), ERK1/2 (70, 71), and STAT3 pathways (34, 72). The VEGF signaling pathway in EPCs plays important potential roles in the regulation of redox homeostasis, cell survival, cell migration, angiogenesis, and vascular regeneration (68).

## TNF $\alpha$ Signaling Pathway

The TNF $\alpha$ /TNFR1 axis mediates post-MI cardiac dysfunction, while the TNF $\alpha$ /TNFR2 axis activation confers protection to ischemic hearts (73). TNF $\alpha$  binding to TNFR2 on EPCs activates the NF- $\kappa$ B signaling pathway to induce increased EPC migration *in vitro* (74). The TNF $\alpha$ /TNFR2 axis *in vivo* has been shown to be critical for ECFC survival, mobilization, and differentiation; VEGF expression; and ischemia-induced neovascularization (75). Naserian et al. found that EPCs modulated T-cell proliferation and acquisition of the proinflammatory phenotype, TNF $\alpha$  enhanced the immunomodulatory effect of ECFCs in an inflammatory environment, and the TNF $\alpha$ /TNFR2 signaling pathway enhanced the production of the anti-inflammatory cytokines TGF $\beta$ , IL-10, and HLA-G (76). In EPCs stimulated with TNF $\alpha$ , activation of the STAT3 signaling pathway through IL-10 overexpression enhanced EPC migration, adhesion, and tubule formation (77). These findings suggest that the TNF $\alpha$ /TNFR2 signaling pathway promotes the proliferation and migration of EPCs and has a cardioprotective effect in ischemic heart injury and MI.

## The Sonic Hedgehog Signaling Pathway

The Sonic Hedgehog (SHH) signaling pathway is a key regulator of postnatal angiogenesis and plays an important role in maintaining vascular homeostasis and angiogenesis (78). The Shh protein can stimulate BM-EPC proliferation and migration and VEGF production, which may promote angiogenesis in ischemic tissues (79). High-throughput RNA-sequencing and semiquantitative proteomic analysis have revealed that Hedgehog-interacting protein (HIP) expression was upregulated



in late EPCs and inhibited hedgehog signaling. Activation of the Shh pathway after HIP expression downregulation during angiogenesis and oxidative stress enhanced angiogenesis and the function of newly sprouted aorta consisting of late EPCs (80). The Shh pathway was activated under hypoxia and oxidative stress, and the delivery of Shh protein enhanced EPC survival, migration, and tube formation (81). Carlos et al. found that microparticles carrying sonic hedgehog morphogen (MPShh+) significantly increased the expression of Shh signaling pathway genes and proangiogenic genes in EPCs, while Shh pathway-induced PI3K activation increased eNOS protein expression and activity, resulting in increased NO production. Most importantly, MPShh+ increased the angiogenic capacity of *in vitro* cultured

EPCs of AMI patients to levels similar to those of healthy patients (82).

## The Notch Signaling Pathway

Notch signaling is involved in vascular development and affects EPC function in the BM microenvironment (83). Mammals express four Notch receptors (Notch 1 to 4) and five Notch ligands (Delta-like 1, 3, 4 and Jagged 1, 2) (84). EPC proliferation, migration and differentiation in the BM niche was stimulated by Jagged 1, but not Delta-like 1, contributing to post-ischemia angiogenesis (85). The regulatory mechanism of EPC homing and angiogenesis has been linked to the Notch pathway (37). Transforming growth factor- $\beta$ -inducible protein-stimulated EPCs activated the NF- $\kappa$ B signaling pathway, inducing the expression of Notch ligands (delta-like 1 and Jagged1). Simultaneous activation of the Notch signaling pathway in adjacent EPCs stimulated the differentiation of EPCs into ECs (86). Guo et al. overexpressed hNotch1. The ICN gene in EPCs activated the Notch 1 signaling pathway and downstream effector molecules Hes1 and Hey1, enhancing the ability of EPCs to adhere to the endothelium, migrate across the endothelium, and form tubes (87). Li et al. studied a MI model and found that deer antler activated the Notch signaling pathway in EPC, upregulated the protein expression of Jagged 1, Notch1, NICD and HES1 and the mRNA expression of Hes1 and Hey2; it also promoted the mobilization of EPCs, endothelial repair and angiogenesis after MI (88).

## Crosstalk Between EPCs and Cardiac Cells During Cardiac Remodeling and Repair

The adult heart is composed of a heterogeneous cell populations comprising 11 major cell types: atrial CMs, ventricular CMs, CFs, ECs, pericytes, SMCs, immune cells (myeloid and lymphoid cells), adipocytes, mesothelial cells, and neuronal cells (89). EPCs promote cardiac repair through direct cell contact and autocrine, and paracrine effects (90). EPC crosstalk with cardiac cell populations promote angiogenesis, improve cardiac microenvironment homeostasis, alleviate adverse remodeling after infarction, and enhance ventricular function (**Figure 2**, **Table 2**).

## Endothelial Cells

ECs form a monolayer on the blood vessel wall and mediate the exchange of molecules between the blood and surrounding tissues and maintain the homeostasis of blood vessels (104). EPCs are precursors of ECs, and BM-EPCs can migrate to sites of ischemic injury, integrate into the original vasculature, differentiate into ECs, and restore the integrity of vascular ECs and their functions (25, 105). On the other hand, EPC-derived anti-apoptotic and pro-angiogenic factors (such as IGF, VEGF, FGF-2, HGF, and SCF) and anti-inflammatory factors stimulate the original ECs and promote new blood vessel formation (91).

EC dysfunction is defined as a state in which reduced NO bioavailability and increased ROS-related oxidative stress cause impaired vasodilation and promote inflammation and coagulation (106). EPCs have been shown to express eNOS, and activated eNOS promotes NO production to prevent EC damage

(107). In ischemic or inflammatory tissue microenvironments with elevated ROS levels, the expression of catalase, copper-zinc superoxide dismutase (Cu/ZnSOD), manganese superoxide dismutase (MnSOD) and anti-apoptotic factor Bcl-2 in EPCs was increased, supporting the supposition that ECs are resistant to ROS-induced toxicity, thereby maintaining their viability and functional activity (26). In addition, recent studies have shown that the endothelial-mesenchymal transition (EndMT) is an important process in vascular endothelial injury and is closely related to plaque stability and endothelial microenvironment homeostasis in coronary atherosclerosis (108). The EndMT causes ECs to lose their endothelial characteristics and acquire a mesenchymal-like cell (SMC and fibroblast) phenotype (109, 110). EPCs undergo the EndMT to differentiate into smooth muscle-like cells after treatment with TGF $\beta$ , and TGF- $\beta$  exacerbates promotes cardiac fibrosis by inducing the EndMT (109, 111). Zhang et al. found that overexpression of miR-126 inhibited the EndMT of EPCs, suggesting that intimal hyperplasia in CAD is inhibited through the EndMT (92). Moreover, the upregulation of miR-221 expression repressed the EndMT of EPCs, possibly by interacting with PTEN to regulate FoxO3a signaling, and promoted EPC acquisition of the endothelial phenotype (93).

Numerous studies have confirmed that EPCs and EPC-extracellular vesicle (EV)-carried miRNAs have angiogenic/vasculogenic properties (112). Templin et al. isolated CD34+ cells from patients with acute ST-segment-elevation myocardial infarction (STEMI) and found that miR-378 expression was significantly upregulated and may have promoted angiogenesis through paracrine vascular growth factor signaling (94). Overexpression of miR-326-5p and miR-126-3p in EPCs significantly promoted tubular structure formation and angiogenesis. Furthermore, miR-326-5p- and miR-126-3p-overexpressing EPCs transplanted into an AMI animal model promoted a significant increase in angiogenesis in the area surrounding MI-damaged tissue and improved left ventricular hemodynamic function (36, 95). EPC-MV-carried miR-126 attenuated ROS-induced vascular endothelial injury and EC apoptosis in a hypoxia/reoxygenation (H/R) injury model (27). In addition, the content of EPC-EVs changes under inflammatory conditions and impairs the repair ability of EPC-EVs in ischemic heart tissue. Yue et al. found specific enrichment of integrin-linked kinase (ILK) and miR-375 in IL-10KO-EPC-Exos by IL-10 knockout mimicking systemic inflammatory conditions. By knocking down ILK and miR-375 in IL-10KO EPC-Exos, NF- $\kappa$ B activation was inhibited in endothelial cells, and the inflammation-induced apoptosis and angiogenic capacity of EPCs and ECs were rescued (96, 97).

## Smooth Muscle Cells

Mature vasculature requires ECs and SMCs, while angiogenesis requires dynamically regulated interactions between ECs, SMCs, and angiogenic factors (96). After vascular injury, EPCs regulate the proliferation, migration, secretion capacity, and phenotypic switching of SMCs, promoting SMCs to form neointima (97). Coculturing EPCs with SMCs induced neovascular development

**TABLE 2** | EPC interactions with cardiac cell populations and mesenchymal stem cells in ischemic heart disease.

Targeted cell type	EPCs/EPC-EXs	Factors	Mechanism	Function	References
ECs	EPCs	IGF, VEGF, FGF-2, HGF, SCF	-	Reduces apoptosis and promotes angiogenesis in HUVECs	(91)
ECs	EPCs	Cu/ZnSOD, MnSOD, catalase, Bcl-2	-	Enhances HUVECs resistance to ROS toxicity and anti-apoptosis	(26)
ECs	EPCs	miR-126	PIK3R2/PI3K/Akt signaling pathway	Inhibits the EndMT process of TGF $\beta$ -induced EPCs	(92)
ECs	EPCs	miR-221	PTEN/FoxO3a signaling pathway	Inhibits the EndMT process of TGF- $\beta$ -induced EPCs	(93)
ECs	EPCs	miR-378	-	Promotes migration and angiogenesis of HUVECs	(94)
ECs	EPCs	miR-326-5p	Wnt1	Enhances the incorporation of EPCs into tubular structures formed by HUVECs <i>in vitro</i> , increases angiogenesis, improves LVEF and reduces myocardial fibrosis <i>in vivo</i>	(36)
ECs	EPCs	miR-126-3p	-	Reduces the expression of inflammatory factors and promote angiogenesis	(95)
ECs	EPC-EXs	miR-126	PI3K/eNOS/NO signaling pathway	Attenuates ROS-induced ECs damage and apoptosis	(27)
ECs	IL-10KO-EPC-Exs	ILK	NF-kB signaling pathway	Enhances inflammatory response and inhibit ECs angiogenesis	(96)
ECs	IL-10KO-EPC-Exs	miR-375	PDK-1/AKT signaling pathway	Promotes apoptosis of ECs and attenuates angiogenesis	(97)
SMCs	EPCs	SDF1 $\alpha$ , VEGF, HGF, TGF $\beta$	-	Stimulates angiogenesis and cardiomyocyte proliferation	(98)
CMs	EPCs	NRG1	PI3K/Akt signaling pathway	Reduces apoptosis and increases proliferation of human pluripotent stem cell-derived cardiomyocytes	(30)
CFs	EPC-EXs	miR-1246/ miR-1290	ELF5/SP1	Promotes MEndT in CFs, promotes angiogenesis, improves cardiac function and reduces cardiac fibrosis	(99)
CFs	EPC-EXs	miR-218-5p/miR-363-3p	p53/JMY	Promotes MEndT in CFs, promotes angiogenesis, improves cardiac function and reduces cardiac fibrosis	(100)
CFs	EPC-EXs	miR-133	-	Promotes MEndT in CFs, promotes angiogenesis	(28)
CFs	EPC-EXs	Shh	Shh signaling pathway	Mediates the transdifferentiation of resident CFs into ECs	(101)
CPCs	EPCs	VEGF, SDF-1, IGF-1	-	Enhances the migration of mature ECs and tissue-resident CPCs.	(102)
MSCs	EPCs	connexin 43, integrin alpha-5	-	Enhances the survival and therapeutic properties of MSCs	(103)

of capillary networks and prevascularized structures, enhanced angiogenic responses and induced the formation of mature blood vessels (113). The interaction between EPCs and SMCs stimulated a massive release of SDF1 $\alpha$ , VEGF, HGF, and TGF $\beta$ , which stimulated CM proliferation and angiogenesis (113). EPC and SMC bilayer cell sheets were transplanted into MI rats, and the interaction of these two cell types in the animal model enhanced arterialization, thereby reducing myocardial fibrosis and adverse remodeling after MI (113, 114). A similar study showed that a bilayer of EPCs and SMCs also attenuated cardiac fibrosis and ventricular remodeling in diabetic cardiomyopathy and improved cardiac function (98).

## Cardiomyocytes

CMs constitute the major cell type lost during ischemia, MI and heart failure; however, CMs show a limited ability to proliferate, and adults exhibit low turnover rates of newly formed CMs, ~0.5–2% per year (115). Current therapeutic goals involve reducing myocardial fibrosis, alleviating myocardial cell dysfunction, and promoting myocardial regeneration. In a myocardial ischemia–reperfusion model, EPCs and EPC-derived conditioned medium enhanced tissue regeneration and improved ischemia-related organ dysfunction by inhibiting oxidative stress (oxidative proteins and markers of oxidative stress), autophagy (LC3B-I and LC3B-II), apoptosis (cleaved

caspace 3 and cleaved PARP) and fibrosis (Smad3 and TGF- $\beta$ )-associated marker expression (116). Studies have shown that miR-214 expression was upregulated in EPCs and may have regulated CM Ca<sup>2+</sup> homeostasis and cell survival during myocardial ischemia injury through miR-214 (117, 118). Hong et al. found that crosstalk between ECs and CMs was critical for regulating CM function and that vascular networks generated by ECFCs enhanced the engraftment of human pluripotent stem cells. The cardioprotective factor NRG1, which is highly expressed in ECFCs, exhibited high paracrine signaling for differentiation of human pluripotent stem cell-derived CMs by activating the PI3K/Akt signaling pathway (30).

## Cardiac Fibroblasts

CFs are essential for cardiac tissue structural remodeling; cardiac chemical, mechanical and electrophysiological properties; and angiogenesis (119). After cardiac injury, CFs transdifferentiate into myofibroblasts and simultaneously trigger the secretion of high levels of extracellular matrix components such as type I collagen, type III collagen, elastin (such as  $\alpha$ -smooth muscle actin), fibronectin, and fibrin, leading to the destruction of normal myocardial structure and increased fibrosis (120). Fibroblasts acquire endothelial-like functions through the mesenchymal-endothelial transition (MEndT) and participate in angiogenesis in damaged heart areas, reversing myocardial fibrosis (121).

EXs derived from EPCs induced the upregulated expression of MEndT-related genes and reduced high mobility box 1 protein B1 expression to promote CF differentiation into ECs (122). Reduced basic fibroblast growth factor and increased angiogenesis in ischemic hearts after EPC EX treatment reduced the area of cardiac fibrosis. Therefore, it was inferred that the proangiogenic function of EPC-derived EXs may be partially attributable of the activated MEndT of CFs (117). However, how EPC-derived EXs regulate the MEndT has not been elucidated to date. By performing a microarray analysis, Huang et al. found differential expression of miRNAs in EPCs and EPC-derived EXs carrying miR-1246 and miR-1290 targeted the binding of the transcription factors ELF5 and SP1 in fibroblasts, inducing endothelial marker CD31 expression (123). In a prior study, p53 signaling was found to activate fibroblast MEndT, enhance vascularity, and improve cardiac function (121). Ke et al. found that EPC-EV-derived miRNAs, specifically the upregulated expression of p53 by miR-218-5p and the downregulated expression of JMY by miR-363-3p, might have alleviated myocardial fibrosis and improved cardiac function by inducing the MEndT to increase angiogenesis (124). Lin et al. performed YBX-1-mediated sorting of miR-133 into H/R-induced EPC-derived EXs and found that they increased fibroblast angiogenesis and the MEndT rate (28). Interestingly, EXs containing Shh protein secreted by Shh-modified CD34+ cells may have mediated the transdifferentiation of resident fibroblasts to ECs by activating the Shh signaling pathway (99). Additionally, Cao et al. found that fibroblasts were efficiently transformed into cardiomyocyte-like cells after reprogramming, providing new insights into cardiac regeneration therapy (100).

## Cardiac Progenitor Cells

A population of resident cardiac stem cells, namely, CPCs, has been isolated from percutaneous endomyocardial biopsy specimens and they showed the potential to differentiate into CMs, SMCs, and ECs (101). Partially through the endogenous repair program in the heart and possibly through the activation of endogenous CPCs and CM proliferation, lost CMs are replaced with new cardiomyocytes to promote the recovery of cardiac function (125). Soluble factors released by EPCs promoted the mobilization and recruitment of circulating and tissue-resident progenitor cells into ischemic tissue under ischemic hypoxic pathological conditions and supported tissue-resident cell (such as mature EC or CPCs) survival and function through paracrine signaling (29). Balbi et al. found that the human amniotic fluid stem cell secretome induced the activation of endogenous epicardial progenitor cells and Ca<sup>2+</sup>-dependent angiogenesis in ECFCs after ischemia-hypoxia injury (126). Deutsch et al. found that ECFC treatment stimulated robust endogenous angiogenesis in Sca-1+ cardiac progenitors, which was accompanied with an increase in the blood vessels formed following infusion of ECFCs into—ischemic myocardium, while an increase in Sca1+ cardiac-resident progenitors was involved in adverse remodeling after MI (127). In another study, engraftment of T $\beta$ 4-treated diabetic EPCs significantly increased the capillary density and attracted an increasing number of c-Kit-positive progenitors into the infarcted heart to enhance repair mechanisms (128).

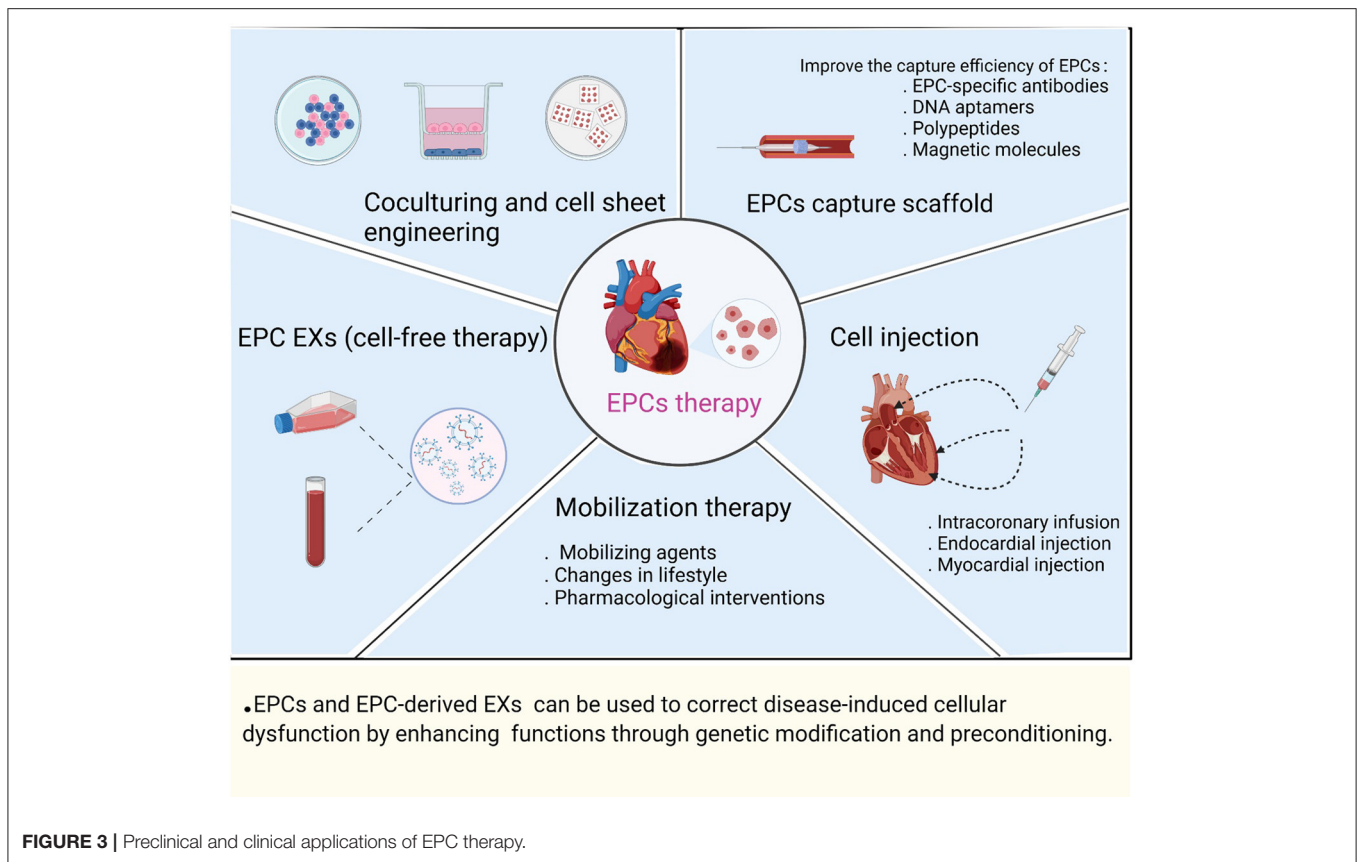
## Crosstalk Between EPCs and MSCs

MSCs are adult stem cells derived from BM and show multidirectional differentiation potential. In the treatment of CVDs, MSCs have the ability to differentiate into CMs and vascular system cells and exert anti-inflammatory, antifibrotic and proangiogenic effects (102, 129). Crosstalk between MSCs and EPCs enhances cardiac repair and cardiac function after MI through paracrine signaling and direct cell contact (130, 131). On the one hand, coculturing MSCs and EPCs enhanced the therapeutic properties of the MSCs, and up-regulation of connexin 43 and integrin-5 expression promoted local intercellular communication and increased MSC engraftment integration capacity (132). Paracrine factors in EPCs stimulated MSCs while maintaining the adhesion and proliferation properties of ECs, thereby supporting efficient angiogenesis (133). On the other hand, coculturing enhanced the angiogenic properties of the EPCs. Both MSCs and EPCs secrete angiogenic factors; however, MSCs secrete additional proangiogenic factors (VEGF and IGFBP-3) that promote the migration, invasion and angiogenesis of EPCs (132).

## The Application and Limitations of EPC Therapy and Clinical Translation

Clinical studies have demonstrated that EPCs can be used as biomarkers of CVD progression and risk, while transplanted EPCs exert paracrine-signaling-induced effects on vascular remodeling, angiogenesis, and tissue repair in the treatment of ischemic disease. The main applications of EPC therapy are currently involve: (1) mobilization therapy; (2) EPC capture





scaffolds; (3) cell injection; (4) coculturing and cell sheet engineering; and (5) EPC EXs (cell-free therapy) (Figure 3).

EPCs are sources of endogenous repair cells, the number and functional activity of EPCs are regulated by cardiovascular risk factors, and the mobilization of EPCs can be regulated by interventions such as treatment with various mobilizing agents (chemokines, growth factors, and cytokines), changes in lifestyle (appropriate physical activity, diet, and smoking cessation) and pharmacological interventions (8, 103, 134, 135). To ensure successful EPC engraftment and promote rapid endothelialization, circulating EPCs can be captured by an EPCs scaffold; that is, EPCs bind to the scaffold surface, and then, the EPCs differentiate into a functional endothelial layer (136). To date, EPC-specific antibodies (monoclonal antibodies against CD133, CD34, and CD146), aptamers (DNA aptamers), polypeptides (Arg-Gly-Asp peptides), and magnetic molecules (superparamagnetic iron oxide nanoparticles) have been widely used in cardiovascular biomaterials to improve the therapeutic effect of EPC capture scaffolds (137). Multiple research groups have evaluated the safety and feasibility of EPCs via endocardial injection, direct injection into the infarcted myocardium, and intracoronary infusion in CVD (angina, MI, and heart failure) (138–140). Stamm et al. found that injection of purified CD133+ progenitor cells into the myocardial infarct border zone during CABG found that left ventricular ejection fraction (LVEF) was significantly higher in the CABG and cell combination treatment

group than in the CABG-only group after 6 months (139). Salvatore et al., studying intracoronary infusion of CD34+ cells in patients with end-stage diffuse CAD who were not candidates for coronary interventional therapy, performed a 5-year follow-up to evaluate the potential of CD34+ cell therapy in improving left ventricular function, heart failure, and cardiac remodeling (140). They found that cell sheet engineering of bioengineered tissues in the repaired heart led to more efficient cell delivery than intracoronary or myocardial injection (141). The implantation of double-layered cell sheets constructed by coculturing EPCs with SMCs or MSCs improved the ability of tissues to form capillary-like networks and a functional vascular bed, while coculturing stimulated mutual paracrine effects to enhance cell survival and differentiation (113, 114, 132). New regenerative medicine approaches were used to treat CVDs through cell-free therapy by exploiting the paracrine signaling mechanisms of stem and progenitor cells, EXs derived from EPCs that carry proangiogenic and cardioprotective cargo, and transplantation of EPC EXs to promote myocardial angiogenesis and recovery of cardiac function after infarction (142). Chen et al. demonstrated sustained delivery of EPC-derived EVs to the ischemic myocardium via injectable hydrogels in a rat model of MI, followed by uptake by ECs, increased vascular density in the infarcted area, and improved cardiac hemodynamics and cardiac reshaping (143). The successful regeneration capacity mediated through cell therapy requires consideration of key factors such

as the source of the transplanted cells, dose of the cells, efficacy of the cells, delivery time, and route of administration (144). Currently, EPCs are inconsistently defined, and therefore, the cell types used in clinical trials vary, particularly in terms of cell isolation, culturing methods, and characterization of cell surface markers. In addition, the cell dose and route of administration vary from trial to trial, making it difficult to compare results from different clinical trials (145). Studies have shown that obtaining sufficient ECFCs from PB is difficult in many cases; however, ECFCs isolated from umbilical cord blood show high proliferative potential and contain relatively high levels of telomerase activity to prevent aging (10). Human induced pluripotent stem cells can reproducibly form isolated homogeneous and stable populations with umbilical cord blood ECFC properties, which include high proliferative and no teratoma-forming potential (146). In addition, different degrees of tissue ischemia, hypoxia, inflammation, and oxidative stress in ischemic diseases cause EPCs to exhibit reduced proliferative capacity, dysfunction, and reduced angiogenic capacity, resulting in a low survival rate of transplanted cells in host tissues (147). EPCs and EPC-derived EXs can be used to correct disease-induced cellular dysfunction by enhancing *in vivo* functions through genetic modification and preconditioning. For example, the combination of gene modification realized by overexpressing genes such as the miR-326-5p (36), miR-126-3p (95), sonic hedgehog (99), and IL-10 (77) genes in EPCs and subsequent EPC transplantation into AMI animal models was found to be significantly correlated with EPC function and cardiac function recovery. Treatment with high-dose statins before PCI promoted an increase in EPC abundance (148). Thymosin  $\beta$ 4 preconditioning enhanced the survival and angiogenic capacity of EPCs during MI and enhanced the repair of the infarcted myocardium (149).

## CONCLUSION

Accumulating evidence suggests that EPCs are important players in endothelial dysfunction repair and angiogenesis, offering great promise for the treatment of CVD. On the one hand, EPCs promote angiogenesis and vascular remodeling in ischemic tissue and accelerate the process of IHD repair. On the other hand, the

paracrine mechanism of EPCs improves the microenvironment after myocardial infarction, enhances cardiac remodeling and repair, and improves cardiac function. In recent years, great progress has been made in research on the role of EPCs in ischemic heart disease, stroke, pulmonary hypertension, and diabetes. However, there are some pressing issues that need to be addressed in future research and clinical trials. How can EPCs be used to establish clear/uniform criteria for definition, separation and quantification? How do circulating EPCs precisely and specifically target ischemic and damaged tissue? How can EPCs reduce the negative effects of ischemia, hypoxia, inflammation, and oxidative stress in disease settings? The paracrine signaling mechanism of EPCs, which comprises a complex network of crosstalk with other cardiac cell types and stem progenitor cells, serves an important repair function; however, the mechanisms of action of specific paracrine components (cytokines, proteins, and miRNAs), the specific cells targeted by EPCs, and the communication and signal transduction mechanisms between EPCs and other types of cells have not been fully elucidated. Therefore, further studies on the molecular mechanisms of these biological processes are expected to contribute to the translation of EPC therapy to the practice of precision medicine.

## AUTHOR CONTRIBUTIONS

HH wrote the manuscript and figure legends and created the figures and tables. WH revised the manuscript. All authors contributed to the article and approved the submitted version.

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