Chapter 2:

Cardiac Progenitor Cells in Various Cardiovascular Diseases

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Abstract

Cardiac ischemic diseases, especially myocardial infarction, are the main cause of human mortality and morbidity. Due to the irreversible tissue changes and lack of function in the affected area, rapid and timely medications and therapeutic protocols are mandatory to reduce post-myocardial infarction complications. Despite the magnificent progress in the health care system and therapeutics, the existence of unwanted side effects necessitates the development of novel medications. In this regard, enormous studies have been done to find highly efficient approaches with minimal complications in patients with myocardial infarction. Cardiac progenitor cells have been discovered in the heart within recent decades, with significant regenerative outcomes. Whether and how these cells can orchestrate the regeneration of ischemic myocardial tissue is at the center of the debate.

Keywords: Cardiac progenitor cells; Cardiac ischemic changes; Cardiac regeneration; Angiogenesis; Regenerative Medicine.

1. Introduction

The changes in lifestyle and nutritional habits have led to the emergence of specific pathological conditions [1]. Among these pathologies, MI[1] and cardiac ischemic changes have increased during the last decades [2]. According to released data, about 19.1 million deaths have been recorded due to cardiovascular disease, with an adjusted death rate of 239.8 per 100,000 individuals [3]. It has been documented that the direct involvement of the coronary artery is the main cause of cardiac ischemic changes and MI [4]. The significant reduction or sudden interruption of blood perfusion into the myocardium leads to the promotion of ischemic and necrotic changes in cardiac cells [5, 6]. From the clinical aspect, symptoms such as individual discomfort with or without dyspnea, the existence of nausea, and/or diaphoresis are clinically manifested. The changes in ECG[2] parameters and elevation of specific factors such as

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[1]. Myocardial infarction

[2]. Electrocardiography

troponin I, CK-MB[1], and prohormone NT-proBNP[2] are also indicative [7]. In cases with bulk involvement of cardiac tissue, complications such as rupture of the ventricular septum, LV[3] damage, and damage to papillary muscles can predispose to mitral dysfunction, ventricular aneurysm, arrhythmias, edematous changes in pulmonary tissue, pericarditis, etc. [8-10]. Along with these changes, massive ischemic changes and cardiomyocyte necrosis increase the possibility of aberrant remodeling in the myocardial wall, leading to a large amount of collagen deposition in the affected areas [11, 12]. The replacement of natural cardiomyoblasts with fibroblasts and transition into the myofibroblasts can lead to massive ECM[4] deposition and separate focal ectopic beating activity [13]. Along with these changes in tissue and molecular levels, cardiac tissue parameters such as ejection fraction, which is clinically determinant of heart failure [14]. Even though myocardial wall rupture causes an increase in MI mortality in the hospital setting. The concomitant increase of specific factors such as CRP[5] and troponin can also be indicative [15]. In the present time, therapeutic strategies such as application of anti-coagulants (aspirin), β blockers, statins, nitrates (nitro-glycerin, etc.), along with re-establishment of blood perfusion using CABG[6] or PCI[7] are available therapeutic options for MI patients [16]. Although recent advances in surgical approaches, the diagnosis, and application of certain pharmaceutics have led to improvement in the care system and identification of vulnerable individuals with MI, the detection and

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[1]. Creatine phosphokinase
[2]. N-terminal prohormone of brain natriuretic peptide
[3]. Left ventricular
[4]. Extracellular matrix
[5]. C-reactive peptide
[6]. Coronary artery bypass graft surgery
[7]. Percutaneous intervention

development of *de novo* therapeutic systems with better regenerative outcomes are mandatory in MI cases [16]. Based on the clinical data, massive bleeding during and after surgical approaches is the main problem related to the current therapeutic protocols [17]. The uncontrolled use of anti-coagulants can increase the bleeding risk in MI individuals [18]. Commensurate with these comments, the application of new therapeutics is mandatory in patients with MI.

In recent years, the discovery of stem cells and the use of stem cell byproducts have led to the alleviation of different cardiac tissue injuries (**Figure 1**) [19]. These cells are isolated from different tissues with the potential to give rise to the various cell lineages [20]. Besides, the secretion of diverse cytokines and growth factors can contribute to the proliferation of injured cardiomyocytes and regeneration of infarcted areas [21]. Among varied stem cell types, CPCs[1] encompass a few fractions of all cardiac cells and reside within the heart tissue in different parts such as atrium, ventricles, epicardium, or pericardium [22, 23]. In this chapter, the recent data about the application of CPCs in ischemic heart disease and underlying reparative mechanisms will be discussed.

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[1]. Cardiac progenitor cells

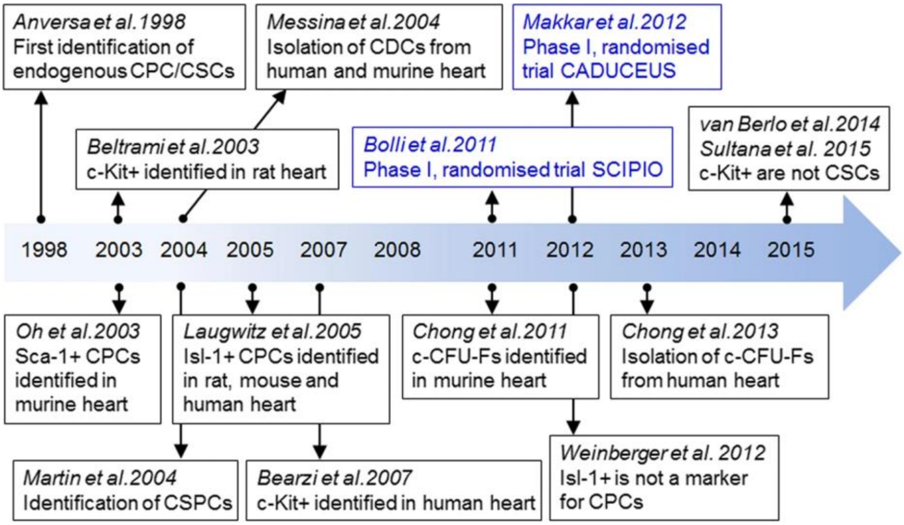

Figure 1. Timeline data related to the discovery of CPCs in humans and other species. Reproduced with permission. [24]. Cell Death Discovery. 2016.

2. Features of CPCs

In the embryonic stage, the heart structure encompasses three progenitor cell types, in which the first progenitor cells originate from epiblasts juxtaposed to the primitive node [25, 26]. These cells can move to the visceral mesoderm along with the primitive streak to produce PHF[1] with the potential to generate cardiac primordia, crescent, and subsequently the LV[2] and atrium. It is believed that the cardiac tube directly originates from the primitive crescent after elongation and looping (**Figure 2**) [25, 27]. The second type of CPCs is named as SHF[3] and are involved in the elongation of heart poles, while these cells can rise to the right ventricle, outflow compartment, and atrial myocardium [26]. Along with PHF and SHF, the last CPC type, known as neural crest cells, make

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[1]. Primary heart field
[2]. Left ventricle
[3]. Secondary heart field

the interventricular septum, pharyngeal arch arteries, valves, and outflow compartment. Of note, these cells can also participate in the development of the cardiac tissue conduction system and innervation [28].

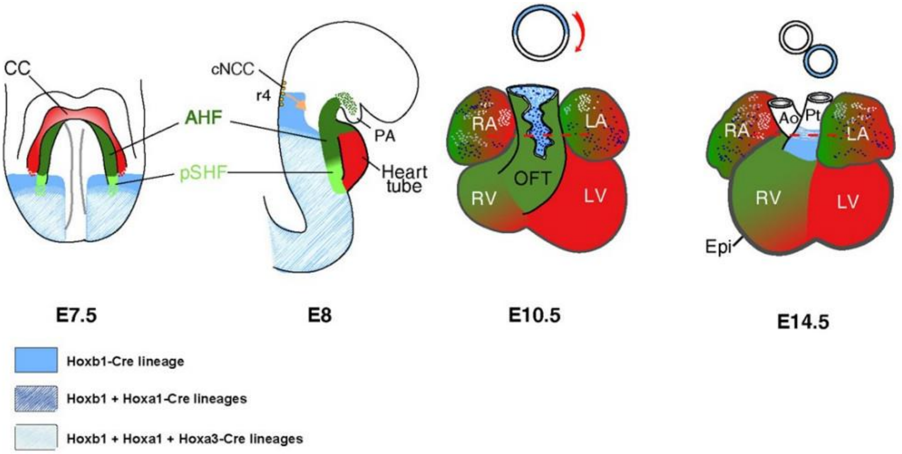

Figure 2. Hox expressing CPCs in the SHF. Illustration indicated stages of cardiac tissue development and contribution of the FHF (red) and SHF (green). Frontal view of embryonic day 7.5 (E7.5), E10.5, E14.5, and lateral view for E8 have been indicated. As SHF CPCs are seen in the elongating heart tube, these cells lead to the formation of the LV, OFT, and right and left atria. The LV is directly derived from the FHF. During E7.5–E8, Hoxa1/b1/a3 expressing cells exhibit subdomains along the anterior-posterior axis of the SHF. After that, Hoxa1/b1/a3 progenitors distribute in the left and right atria and the inferior wall of the OFT around E10.5 with the potential to commit into the subpulmonary myocardium around E14.5. Abbreviations: Anterior heart field: AHF; Aorta: Ao; Cardiac crescent: CC; Cardiac neural crest cells: cNCC; Epicardium: Epi; Left atrium: LA; Left ventricle: LA; Pharyngeal arch: PA; Pulmonary trunk: Pt; Right atrium: RA; Right ventricle: RV; Posterior second heart field: pSHF. Reproduced with permission. [29]. Journal of Cardiovascular Development and Disease. 2014.

Various overlapping morphogenic systems control heart development by organizing transcriptional networks [27]. It has been validated that Isl-1 and Nkx2-5 expression discriminate CPCs following GATA4 activation. GATA4, along with SWI/SNF,[1] induces the specification of CPCs (**Figure 3**) [30]. Additionally, MEF2C[2], HAND1, HAND2, and TBX are other critical

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[1]. Subunit of chromatin remodeling complex

[2]. Myocyte enhancer factor 2C

transcription factors in early CPCs [27, 31]. In the next stages, BMPs (bone morphogenetic proteins), SHH[1], Nodal, NOTCH, retinoic acid, neuregulin, FGFs[2], WNTs, etc., are involved [27]. IGF-bp5, IGF-bp5[3], VEGFR2 (Flk-1/KDR), and transmembrane protein ODZ4 are essential regulatory mediators of cardiogenesis [27].

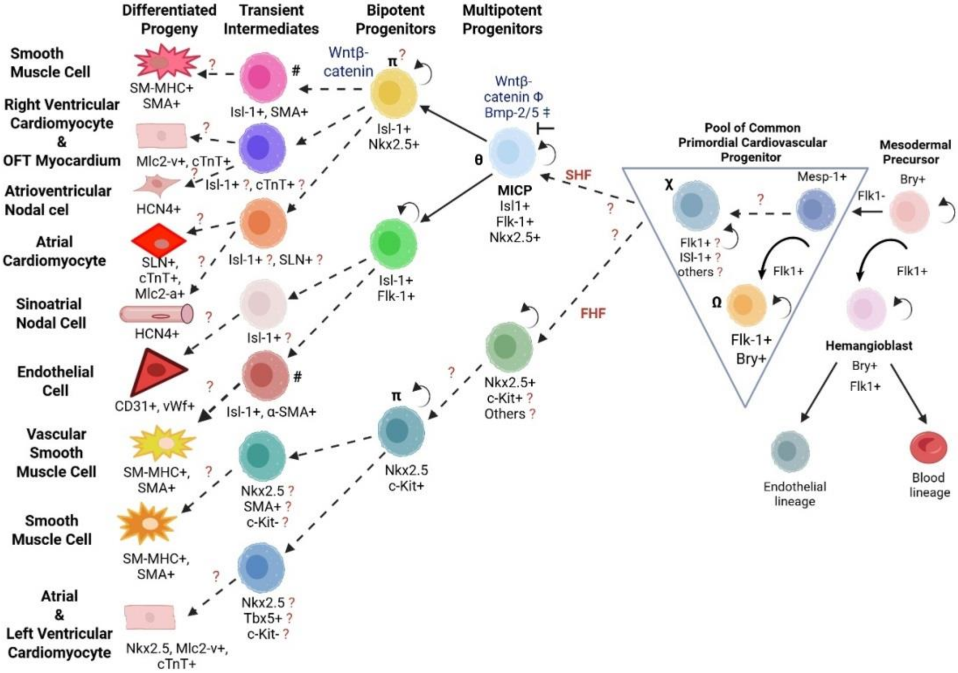

Figure 3. Proposed fate map of mouse CPCs based on available data. Created by Online BioRender software. 2025.

These cells are specific stem cell types within the cardiac tissues, either in embryonic, neonatal, and adult periods [25, 32]. Studies have reported various CPC sub-populations in both developing and adult hearts,

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[1]. Sonic hedgehog

[2]. Fibroblast growth factors

[3]. Insulin-like growth factor-binding protein 5

including CDCs[1], c-kit+ cells, cardiac SP[2] cells, EPDCs[3], Sca-1+[4] CPCs, PDGFRα+[5] expressing CPCs, and Islet-1^{+} expressing CPCs. These CPC sub-populations exhibit the expression of transcription factors like Nkx2.5, Isl-1, GATA4, and MEF2C. Coincidentally, different stemness markers, such as Bmi-1, Oct3/4, and Nanog, have been reported in CPCs [33]. Also, it has been shown that these cells can express several markers such as c-Kit, Sca-1, Isl-1, PDGFR-α, CD44, CD90, CD29, CD105, CD34, Abcg, CD166, and CD46 in humans and rodents (**Table 1**) [34].

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[1]. Cardiosphere-derived cells
[2]. Side population
[3]. Epicardium-derived cells
[4]. Stem cell antigen-1
[5]. Platelet-derived growth factor receptor-alpha

Table 1. CPC sub-population markers in different species

Species					
CPC sub-populations	**Rats**	**Mice**	**Canine**	**Swine**	**Human**
CDCs	CD105^{+}, CD34^{+}, CD45^{+}, Abcg2^{+}, Sca1^{+}, c-Kit^{low} [33], CD31^{+} [34]	CD105^{+}, CD34^{+}, CD45^{+}, Abcg2^{+}, Sca1^{+}, c-Kit^{low} [33], CD31^{+} [34]	CD105^{+}, CD34^{+}, CD45^{+}, Abcg2^{+}, Sca1^{+}, c-Kit^{low} [33], CD31^{+} [34]	CD105^{+}, CD34^{+}, CD45^{+}, Abcg2^{+}, Sca1^{+}, c-Kit^{low} [33], CD31^{+} [34]	CD105^{+}, CD34^{+}, CD45^{+}, Abcg2^{+}, Sca1^{+}, c-Kit^{low} [33], CD31^{+} [34], CXCL6 [35], KDR^{+}, c-KIT$^{+/-}$, CD34^{-}, CD45^{-}, CD133^{-}, NKX2.5^{+}, GATA4^{+}, ISL1^{+}, CD90^{+} [22]
c-kit+	CD34^{-}, CD45^{-}, Sca-1^{+}, Abcg2^{+}, CD105^{+}, CD166^{+}, GATA-4^{+}, NKX2–5$^{+/-}$ or ^{low}, MEF2C^{+}, VEGFR-2^{-}, CD31^{-} [34]	CD34^{-}, CD45^{-}, Sca-1^{+}, Abcg2^{+}, CD105^{+}, CD166^{+}, GATA-4^{+}, NKX2–5$^{+/-}$ or ^{low}, MEF2C^{+}, VEGFR-2^{-}, CD31^{-} [34]	CD34^{-}, CD45^{-}, Sca-1^{+}, Abcg2^{+}, CD105^{+}, CD166^{+}, GATA-4^{+}, NKX2–5$^{+/-\text{ or low}}$, MEF2C^{+}, VEGFR-2^{-}, CD31^{-}, CD90^{+}, Oct3/4^{+}, Bmi-1^{+}, Nanog^{+} [36]	CD34^{-}, CD45^{-}, Sca-1^{+}, Abcg2^{+}, CD105^{+}, CD166^{+}, GATA-4^{+}, NKX2–5$^{+/-\text{ or low}}$, MEF2C^{+}, VEGFR-2^{-}, CD31^{-} [34]	CD34^{-}, CD45^{-}, Sca-1^{+}, Abcg2^{+}, CD105^{+}, CD166^{+}, GATA-4^{+}, NKX2–5$^{+/-\text{ or low}}$, MEF2C^{+}, VEGFR-2^{-}, CD31^{-} [34], Ki67^{+}, GATA4/5^{+}, TBX5^{+}, CD31$^{+/-}$ [22]
SP		CD34^{+}, CD45^{+}, Abcg2^{+}, Sca-1^{+}, c-kit^{+}, NKX2–5^{-}, GATA4^{-} [33]	CD34^{+}, CD45^{+}, Abcg2^{+}, Sca-1^{+}, c-kit^{+}, NKX2–5^{-}, GATA4^{-}, CD90^{+}, Flk-1^{+} [36]	CD34^{+}, CD45^{+}, Abcg2^{+}, Sca-1^{+}, c-kit^{+}, NKX2–5^{-}, GATA4^{-}, ABCG2^{+}, NG2^{+}, SSEA-4^{+} [37, 38]	CD34^{+}, CD45^{+}, Abcg2^{+}, Sca-1^{+}, c-kit^{+}, NKX2–5^{-}, GATA4^{-} [34], CD34$^{+,}$ CD31$^{+/-,}$ c-KIT^{+}, NKX2.5^{+}, GATA4^{+}, MEF2C^{+}, CD45^{-} VE-cadherin^{-} [22]
EPDCs		CD34^{+}, c-Kit$^{+/-}$, CD44^{+}, CD90^{+}, CD105^{+}, CD46^{+}, WT-1 [34]	CD34^{+}, c-Kit$^{+/-}$, CD44^{+}, CD90^{+}, CD105^{+}, CD46^{+}, WT-1, GATA4^{+}, PDGFRα^{+} [35, 36]	CD34^{+}, c-Kit$^{+/-}$, CD44^{+}, CD90^{+}, CD105^{+}, CD46^{+}, WT-1, CD29^{+}, GATA4^{+} [34, 37, 39]	CD34^{+}, c-Kit$^{+/-}$, CD44^{+}, CD90^{+}, CD105^{+}, CD46^{+}, WT-1 [34]
Sca-1^{+}		Sca-1^{+}, CD105^{+}, CD34^{-}, CD45^{-}, FLK1^{-}, c-kit$^{+/-}$, GATA-	Sca-1^{+}, CD105^{+}, CD34^{-}, CD45^{-}, FLK1^{-}, c-kit$^{+/-}$, GATA-	Sca-1^{+}, CD105^{+}, CD34^{-}, CD45^{-}, FLK1^{-}, c-kit$^{+/-}$, GATA-4^{+}, NKX2-5$^{+/-}$,	Sca-1^{+}, CD105^{+}, CD34^{-}, CD45^{-}, FLK1^{-}, c-kit$^{+/-}$, GATA-4^{+}, NKX2-5$^{+/-}$, MEF2C^{+}; CD133^{-} [34], ISL1^{+}, c-KIT$^{+/}$,

		4$^+$, NKX2-5$^{+/-}$, MEF2C$^+$; CD133$^-$ [34]	4$^+$, NKX2-5$^{+/-}$, MEF2C$^+$, CD133$^-$, CD90$^+$, Oct3/4$^+$ [36]	MEF2C$^+$, CD133$^-$, CD90$^+$, CD29$^+$ [34, 37]	PDGFRα$^+$, CD90$^+$, CD44$^+$, TEF-1$^+$, CD31$^{+/-}$, ABCG2$^+$ [22]
PDGFRα+			PDGFRα$^+$, Sca-1$^+$, c-Kit^{low}, CD31$^-$, CD45$^-$, CD90$^+$ [36]	PDGFRα$^+$, CD90$^+$, CD29$^+$, CD44$^+$ [37, 39]	PDGFRα$^+$ [40]
Islet-1$^+$	CD31$^-$, Sca-1$^-$, c-kit$^-$, GATA-4$^+$, NKX2–5$^+$ [34]	CD31$^-$, Sca-1$^-$, c-kit$^-$, GATA-4$^+$, NKX2–5$^+$ [34]	CD31$^-$, Sca-1$^-$, c-kit$^-$, GATA-4$^+$, NKX2–5$^+$, Islet-1$^+$ [36]	CD31$^-$, Sca-1$^-$, c-kit$^-$, GATA-4$^+$, NKX2–5$^+$ [34]	CD31$^-$, Sca-1$^-$, c-kit$^-$, GATA-4$^+$, NKX2–5$^+$ [34]
CFU		Sca-1$^+$, PDGFR-α$^+$, CD31$^-$, c-Kit^{low}, CD45$^-$, FLK1$^-$, CD44$^+$, CD90$^+$, CD29$^+$, CD105$^+$ [34]	Sca-1$^+$, PDGFR-α$^+$, CD31$^-$, c-Kit^{low}, CD45$^-$, FLK1$^-$, CD44$^+$, CD90$^+$, CD29$^+$, CD105$^+$ [41]	Sca-1$^+$, PDGFR-α$^+$, CD31$^-$, c-Kit^{low}, CD45$^-$, FLK1$^-$, CD44$^+$, CD90$^+$, CD29$^+$, CD105$^+$ [42]	Sca-1$^+$, PDGFR-α$^+$, CD31$^-$, c-Kit^{low}, CD45$^-$, FLK1$^-$, CD44$^+$, CD90$^+$, CD29$^+$, CD105$^+$ [34]

Abbreviations: cardiosphere-derived cells: CDCs; epicardium-derived cells: EPDCs; Colony-forming unit: CFU; Side population: SP; Platelet-derived growth factor receptor A: PDGFR; cardiac progenitor/stem cells: CPCs

The niche of stem/progenitor cells is the regional dynamic surrounding microenvironment in which they participate in tissue homeostasis in both physiological (aging and development) and pathological circumstances [43]. The direct cell-to-cell contacts and the paracrine factors expression are considered as two primary sides of the stem/progenitor cell niche functionality (**Figure 4**) [44].

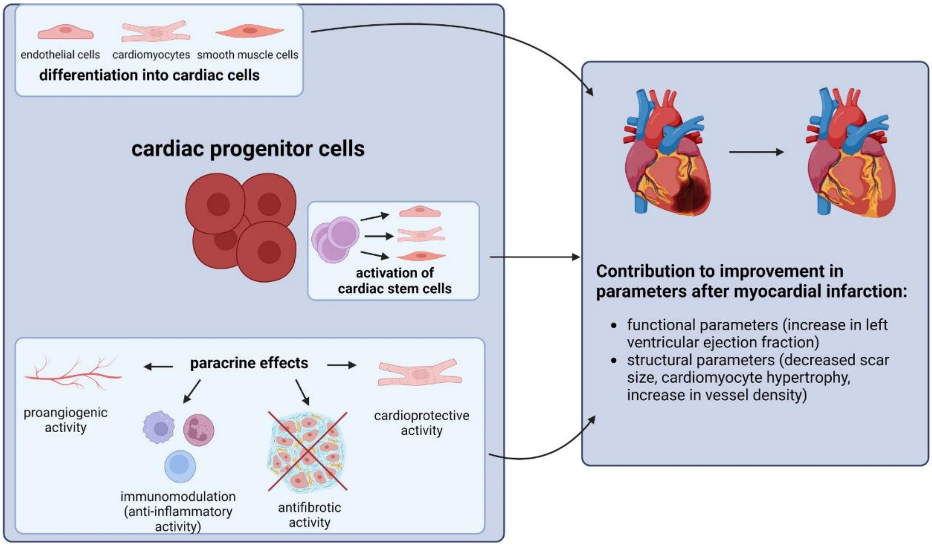

Figure 4. The role of CPCs in heart regeneration under ischemic conditions. CPCs can orchestrate the healing process via direct differentiation into cardiomyocytes, ECs, and α-SMA[1] cells, activation of other CPCs to generate the cardiac cells, and release of angiogenesis factors. It is thought that CPCs can control the extension of inflammatory response and fibrotic changes. Several studies have confirmed the protective role of CPCs under ischemia and myocardial damage. Reproduced with permission. [34]. Cell & Bioscience. 2024.

In the case of CPCs, these cells can interact with each other (isotypic) or other supporting cells (heterotypic), including cardiomyocytes, EC[2], fibroblasts, immune cells, and smooth muscle cells. Cardiomyocytes and

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[1]. Vascular smooth muscle cells

[2]. Endothelial cells

fibroblasts come into contact with CPCs with adhesive molecules like cadherins and connexins. On the other hand, gap junctions between them are applied to transfer information [45]. It has been proven that these two cell types are essential in the differentiation of CPCs and heart fate [46]. Otherwise, CPCs secrete cytokines and growth factors that play a key role in cell survival, proliferation, and inhibition of hypertrophy [47]. According to the presence of CPCs in the perivascular regions, the interaction of CPCs with smooth muscle cells and ECs is possible. The Notch signaling pathway, which is involved in the fate of cells, is assumed to be responsible for these connections. VEGF, as the main mediator of endothelial cells-CPCs interaction, enhances the migration of CPCs and their differentiation into smooth muscle cells and endothelial cells. Macrophages, as a heterogeneous population of immune cells, stimulate the proliferation of CPCs and promote their differentiation to endothelial cells and cardiomyocytes by releasing growth factors like VEGF, IGF-1, and TGF-β [45]. On the other hand, CPCs induce polarization of macrophages from proinflammatory to anti-inflammatory phenotype [48]. CPCs' retention within a pathological and inflammatory circumstance is improved by secreted anti-inflammatory cytokines by natural killer cells (innate immune system effector) and downregulation of their toxicity [45]. Mast cells are similar to CPCs in their position (perivascular area) and expression of markers. However, direct cell-to-cell contact has not been reported yet. TGF-β[1], as an essential component to the differentiation of CPCs, could be released during the degranulation of mast cells (**Figure 5**) [49].

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[1]. Transforming growth factor beta

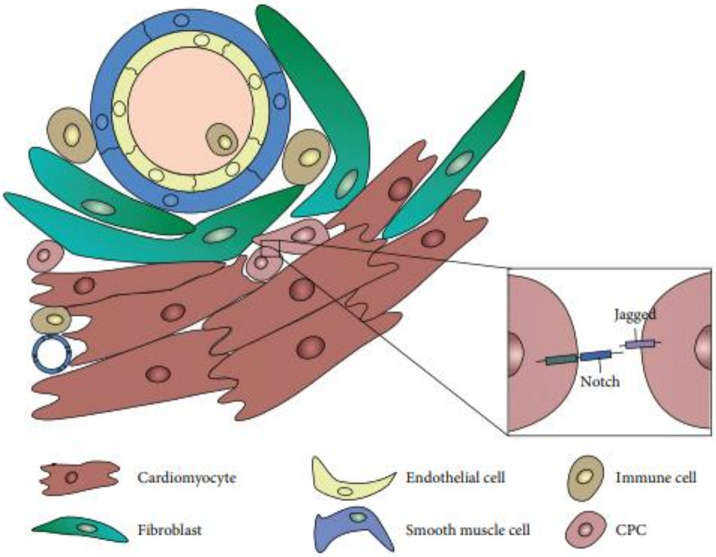

Figure 5. The existence of cell-to-cell interactions in the CPC microenvironment. It is thought CPCs can make juxtacrine (Notch pathway) and paracrine communications with homologous and heterologous cells, including cardiomyocytes, endothelial cells, fibroblasts, smooth muscle cells, and immune cells. Reproduced with permission. [50]. Stem Cells International. 2017.

Cardiac ECM[1], as an important part of the niche, is a dynamic and highly organized network that surrounds cardiac cells [51]. Various proteins, glycosaminoglycans, and proteoglycans, which make a fibrillar supportive network, are involved in cardiac ECM compositions. Cardiomyocytes adhere to their microenvironment via focal adhesions such as integrins (α1β1, α5β1, and α7β1) [45]. It has been proven that stiffness, structure, and/or composition of ECM affect commitment of progenitors [52]. The culture of CPCs in hypoxic conditions (<3%) has upregulated expression of markers related to progenitors like c-KIT and BMI1[2] [53]. Other experimental studies have demonstrated the regulation

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[1]. Extracellular matrix
[2]. Polycomb group RING finger protein 4

of CPCs' behavior and function, like proliferation, cardiogenic gene expression, and cell survival, by ECM [54].

Also, the regional oxygen tension is an important factor in CPCs' survival, migration, genomic stability, cardiac regeneration, and cardiac regeneration [55]. The therapeutic potential of CPCs has been evaluated in many preclinical studies. For example, the injection of adult CDCs into the border zone of cardiac tissue in immunodeficient MI RNU[1] rats led to enhanced LV function and reduction of infarct [56]. In a study conducted by Kanda and co-workers, the cultured Sca-1^+ CPCs in a 3D self-assembling peptide hydrogel contributed to an increased survival rate and even distribution of these cells. Besides, transplantation of CPC laden hydrogel to the pericardial space in MI mice decreased infarct size and ameliorated cardiac remodeling and function [57]. Similarly, CPCs have been used in several large laboratory animal models with the potential to promote cardiac function. For example, c-kit^+ cell administration in a swine model of MI improved the myocardial infarction [58]. Along with direct transplantation of CPCs, some studies have used CPC byproducts, such as CPC[2] EVs, for the alleviation of cardiac cells in *in vitro* and *in vivo* conditions [59].

Several clinical trials have been conducted to date to evaluate the regenerative properties of CPCs in cardiovascular disease patients. Among them, ALLSTAR, with the greatest patient population, is a phase I, II trial used intracoronary allogenic cardiosphere-derived stem cells delivery in patients with ILVD[3]. Based on the obtained data, parameters

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[1]. Charles River's immunodeficient Rowett Nude

[2]. Extracellular vesicles

[3]. Ischemic left ventricular dysfunction

such as LVES[1] and LVED[2] volume were reduced without any positive effects on scar size [60]. In another phase II clinical trial, namely the CONCERT-HF study, the safety, feasibility, and efficacy of c-kit$^+$ CPCs alone and in combination with MSCs[3] were monitored via the trans-endocardial route in patients with heart failure. Data confirmed the eligibility and suitability of this approach for obtaining clinical outcomes with fewer MACE[4] and improving the quality of life. However, LV function and tissue integrity remained unchanged [61]. In the PERSEUS, a phase II trial in patients with HLHS[5], the intracoronary infusion of autologous CDCs led to improved ventricular function and volume enhancement and reduced cardiac fibrosis [62]. Commensurate with these data, it is logical to hypothesize that the regenerative potential of cardiac tissue under insulting conditions, such as ischemia, is mainly because of CPCs. Indeed, CPCs with clonogenic, self-renewing, and multipotent features can mature into functional cardiomyocytes or other cardiac cells, i.e., ECs[6], and α-SMA[7] cells. Additionally, these cells are capable of releasing several cytokines and growth factors to regulate the proliferation of cardiomyocytes and angiogenesis [63]. As mentioned previously, CPCs can regulate apoptosis, inflammation, and fibrotic changes following the occurrence of several injuries. However, cardiac tissue cannot orchestrate the healing process following extensive ischemia or necrotic changes due to a small number of CPCs [34]. Notably, the regenerative mechanism of CPCs is associated with direct differentiation into cardiac cells, including

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[1]. Left ventricular end-systolic
[2]. Left ventricle end-diastolic
[3]. Mesenchymal stem cells
[4]. Major adverse cardiac events
[5]. Hypoplastic Left Heart Syndrome
[6]. Endothelial cells
[7]. Alpha smooth muscle actin

cardiomyocytes, smooth muscle cells, and ECs, proangiogenic, cardioprotective, immunomodulatory, and antifibrotic activities [34, 64]. To this end, the CPC's multilineage differentiation properties have been investigated by several experiments [65-67]. Of course, it should be noted that the number of CPCs differentiating into mature cardiomyocytes in the ischemic zone is too small [34]. Therefore, an additional mechanism may be involved in the acceleration of ischemic myocardium after transplantation of CPCs. It is well proven that CPCs could secrete various bioactive molecules into the surrounding milieu in a paracrine way [68]. The molecular profiling of CPCs' secretome has signified a profile of numerous factors, cytokines, and biological molecules playing a key role in cardiac repair after injury [64, 68]. These components could include SDF-1α[1], SCF[2], Ang-1[3], growth factors like HGF[4], VEGFA[5], IGF-1[6], bFGF[7], and PDGFB[8] [69]. Besides, EVs[9], also known as exosomes, play a significant role in intercellular interactions [70]. The presence of various active substances on the surface of these nanoscale heterogeneous particles, together with rich cargos, makes them influence other cells [71]. CPC Exo[10] secretion has been confirmed by adult human and mouse CPCs' ultrastructure electron microscopy images [71]. CPC Exos could carry genetic materials and other signaling molecules such as DNA, RNA, proteins, and lipids [34]. To be specific, different RNA types, such as miRNAs (miR-126, miR-132, miR-146a, miR-181a/b, miR-210, and miR-

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[1]. Stromal cell Derived Factor 1α
[2]. Stem Cell Factor
[3]. Angiopoietin 1
[4]. Hepatocyte Growth Factor
[5]. Vascular Endothelial Growth Factor A
[6]. Insulin-like Growth Factor 1
[7]. Basic Fibroblast Growth Factor
[8]. Platelet Derived Growth Factor subunit B
[9]. Extracellular vesicles
[10]. Exosomes

935), and mRNAs have been identified inside CPC Exos [72-76]. These bioactive molecules participate in the repair of the heart by affecting cardiomyocyte survival, proliferation, and cardiac hypertrophy [77]. These factors can regulate the activity of cardiac fibroblasts to reduce the collagen fiber deposition [78]. Also, ECs, as a key part of angiogenesis, show enhanced activity with vessel density increase in the presence of secreted compositions [79]. As well, exosomal factors can regulate the function of immune cells to diminish proinflammatory cytokines and control macrophage and neutrophil recruitment into the ischemic sites. Besides, the phenotype acquisition of macrophages into the proinflammatory status is also inhibited in the presence of CPC secretome [74, 80]. EVs as prospective off-the-shelf therapeutics are estimated to be more practicable than whole-cell therapy on account of their biocompatibility, being non-tumorigenic, non-immunogenic, and capable of cargo loading [81, 82]. However, there are some limitations in EV administration in cardiovascular disease. For instance, contamination by bound and co-purified molecules upon isolation and usage of EVs could influence practical assays [83]. Besides, the determination of EVs fraction that is responsible for therapeutic goals is essential due to their heterogeneous nature [84].

3. Conclusion

Because CPCs possess differentiation and paracrine activities to promote the healing of ischemic cardiac tissue, their application opens a way to alleviate several cardiovascular diseases, especially MI. However, due to the limited number of studies related to the application of CPCs in human and animal models, it is recommended to conduct studies with a sophisticated design to address different underlying mechanisms following the administration of CPCs. Parameters such as cell dose, administration rate, dose timing, etc., should also be elucidated.

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