Perspective

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Resident stem cells in the heart

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Abstract: Cardiovascular disease is the leading cause of mobility and morality worldwide, in which the ischemic heart disease is the most common type of the diseases. During last decade, a major progress in the study of the pathogenesis of heart disease has been achieved. For example, the discovery of adult stem/progenitor cells in the heart and vessel tissues may play a role in tissue regeneration. However, the issue of 31 retractions for cardiac stem cell work has caused a "storm of trust" in the heart stem cell field, in which both founders and scientists have become cautious and conservative in stem cell research of the heart. Despite that the existence of adult cardiac stem cells has been denied, recent studies confirmed that there are many other resident stem/progenitor cells in adult heart. Although these cells cannot differentiate into cardiomyocytes, the role they played in heart repair after injury should not be ignored. The purpose of this short article is to briefly review the current research progress in resident stem/progenitor cells in the heart, to discuss how they function during cardiac repair and to point out unanswered questions in the research field.

Keywords: adult heart; ischemic heart disease; resident stem/progenitor cells.

Cardiovascular disease is the leading cause of mobility and morality worldwide, in which the ischemic heart disease is the most common type of the diseases [1]. During last decade, a major progress in the study of the pathogenesis of heart disease has been achieved. For example, the discovery of adult stem/progenitor cells in the heart and vessel tissues may play a role in tissue regeneration [2, 3]. However, the issue of 31 retractions for cardiac stem cell work has caused a "storm of trust" in the heart stem cell field, in which both founders and scientists have become cautious and conservative in stem cell research of the heart. Despite that the existence of adult cardiac stem cells has been denied, recent studies confirmed that there are many other resident stem/progenitor cells in adult heart [3–8]. Although these cells cannot differentiate into cardiomyocytes, the role they played in heart repair after injury should not be ignored. The purpose of this short article is to briefly review the current research progress in resident stem/progenitor cells in the heart, to discuss how they function during cardiac repair and to point out unanswered questions in the research field.

Resident stem cells in the heart

For last decade, it was believed that heart stem/progenitor cells mainly originate from bone marrow and perivascular circulating system. Interestingly, recent studies found that there are many kinds of resident stem/progenitor cells located in the heart tissue. They have been named according to their origins and functions, e.g. endothelial progenitor cells (EPCs), smooth muscle progenitor cells (SMPCs), adipose-derived stem cells (ADSCs), pericytes, mesenchymal stem cells (MSCs), and cardiosphere-derived cells (CDCs). EPC is considered to have the ability to give rise to endothelial cells (ECs). Previous research demonstrated that EPCs mainly derived from bone marrow and peripheral blood circulating system [9, 10]. However, subsequent study showed that EPCs extensively exist throughout the different areas of the blood vessel wall [2, 3]. These results then were confirmed by other research groups [11, 12]. For a long time, the theory of smooth muscle cell (SMC) phenotypic switch plays a dominant role in explaining the SMC proliferation and intima formation during vascular remodeling, [13, 14] while more and more studies reported that smooth muscle progenitors which can differentiate into SMCs widely distributed in the blood vessel [15, 16]. ADSCs were first discovered and defined as MSC isolated from adipose tissue extraction, and these cells have the potential to differentiate into ECs, SMCs, and other cells to participate in cardiovascular regeneration [6]. Cardiac pericytes are abundantly found in the heart, due to their origin from mesenchymal angioblasts during development [17], they are considered to be a group of

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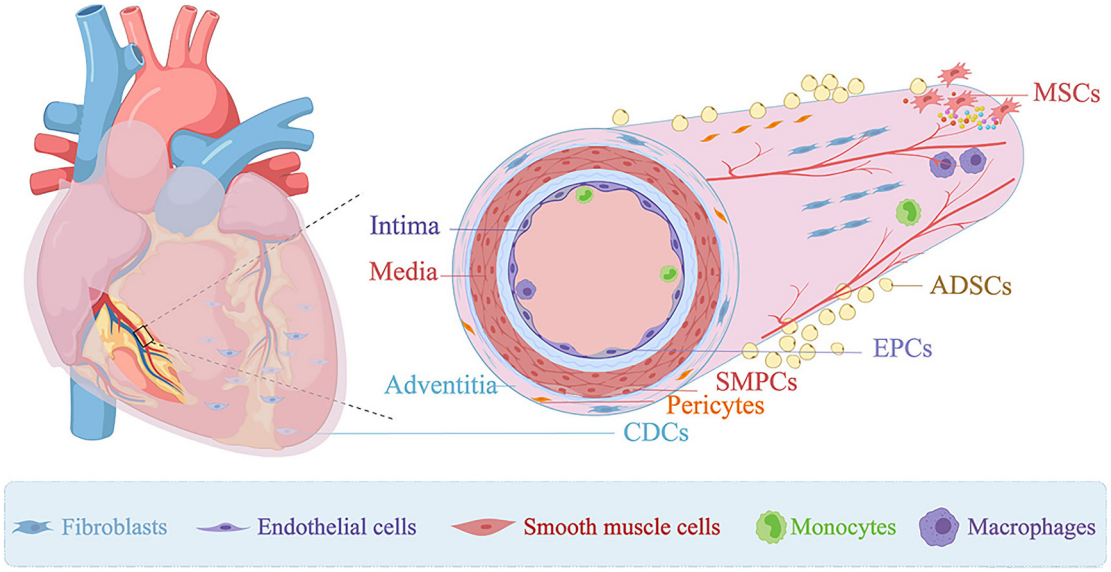

Figure 1: Resident stem cells in the heart. Many resident stem cells, such as EPCs, SMPCs, pericytes, ADSCs, MSCs, and CDCs, are found to be enriched both in perivascular tissue and other cardiac tissues like adipose of the heart. ADSCs: adipose-derived stem cells; CDCs: cardiosphere-derived cells; EPCs: endothelial progenitor cells; MSCs: mesenchymal stem cells; SMPCs: smooth muscle progenitor cells. (Adapted from "Heart", "Muscular artery cross-section with red blood cells", by BioRender.com [2020]. Retrieved from https://app.biorender.com/biorender-templates).

cells with stem cell characteristics in the heart [4]. MSCs (mainly refer to the circulating MSCs) have been tried in many studies to treat cardiac dysfunctions by mechanisms that remain unclear. However, the outcome of the treatment is still controversial. Recent study revealed that there exists a population of tissue-resident but not circulating MSCs in the heart. These resident MSCs possess the ability to generate fibroblasts and even myofibroblasts upon cardiac dysfunction [5]. CDCs, isolated from human myocardial biopsies, were also regarded as a kind of stem cells in the heart based on their expression of stem cell-related antigens and the capacity to differentiate into cardiomyocytes [18]. Thus, different types of stem/progenitor cells may contribute to a variety of cell types in the heart (Figure 1).

Resident stem cells in cardiac diseases

Some of resident stem/progenitor cells are mainly located in the blood vessels and can give rise to vascular cells and inflammatory cells, therefore these cells play crucial roles in the cardiac vascular endothelium repair, vascular remodeling, angiogenesis, inflammation response, and other processes in injured heart. Multiple studies have strongly supported that EPCs help cardiac function recovery by differentiating into ECs to promote endothelium repair and angiogenesis after myocardial infarction (MI) [7, 19]. In addition, progenitors also assist to rebuild impaired heart vascular through differentiation into SMCs. ADSCs were reported to be able to differentiate into ECs and SMCs, which are the main components of the cardiovascular system [3, 20]. Furthermore, ADSCs have the capability of secreting a series of paracrine factors (vascular endothelial growth factor [VEGF], insulin growth factor [IGF]-1, hepatocyte growth factor [HGF], miR31, etc.) and exosomes to reduce cardiomyocyte apoptosis, fibrosis, and anti-cardiac remodeling, which probably accounts for the cardiac regeneration [6]. Cardiac pericytes occupy 5% of the total non-myocyte population [17]. Studies revealed that pericytes contribute to heal heart damage through a variety of ways: differentiating into myofibroblasts to aid in preserving structure, helping revascularization to perfuse the ischemic zones with oxygen and nutrients, and maintaining vascular stabilization by paracrine signaling [4]. Cardiac fibrosis is a process with activation of fibroblasts and accumulation of myofibroblasts coupled with extracellular matrix (ECM) deposition which would eventually result to the heart failure. The traditional view supposed that circulating MSCs are major contributors in cardiac repair. With the development of genetic lineage tracing technology, solid evidence demonstrated that resident MSCs, but not circulating MSCs, are involved in the post-injury myocardial remodeling by regulating

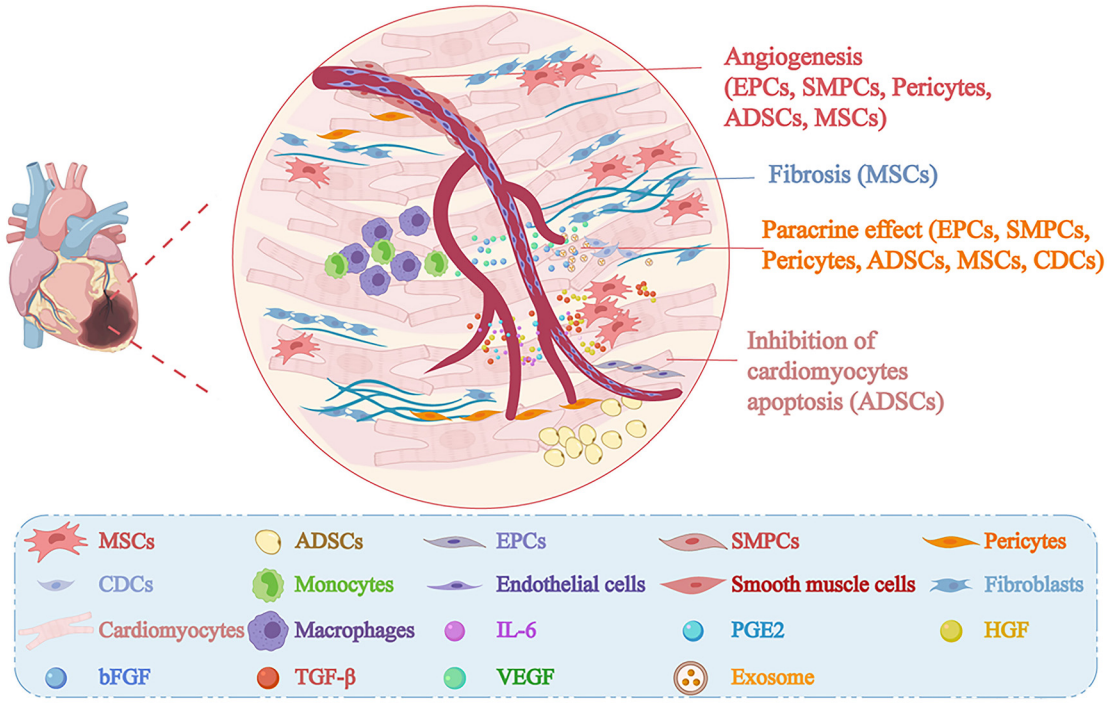

Figure 2: The roles of resident stem cells in cardiac diseases. After injury, these resident stem/progenitor cells not only differentiate into various types of cells to participate in inflammatory response, angiogenesis, and cardiac fibrosis, but also secrete many factors and exosomes to help maintain vascular homeostasis and inhibit cardiomyocyte apoptosis in the process of myocardial repair. ADSCs: adipose-derived stem cells; bFGF: basic fibroblast growth factor; CDCs: cardiosphere-derived cells; EPCs: endothelial progenitor cells; HGF: hepatocyte growth factor; IL-6: interleukin 6; MSCs: mesenchymal stem cells; PGE2: Prostaglandin E2; SMPCs: smooth muscle progenitor cells. TGF-β: transforming growth factor-β; VEGF: vascular endothelial growth factor. (Adapted from "Histological Evolution of Acute Myocardial Infarction", by BioRender.com [2020]. Retrieved from https://app.biorender.com/biorender-templates).

cardiac fibrosis and ventricular function [5]. Although CDCs can differentiate into cardiomyocytes *in vitro*, considering the limited number of cardiomyocytes they give rise to *in vivo*, it was supposed that the beneficial effects of CDCs may be mainly attributed to paracrine effects [21]. Of note, most resident stem/progenitor cells mentioned above can secrete cytokines and exosomes to inhibit myocardial apoptosis and maintain vascular homeostasis so as to promote the repair of injured myocardium. In particular, exosomes play an intriguing role in heart repair via promoting angiogenesis, cardiomyocyte survival, proliferation, etc. [22]. Thus, stem/progenitor cells exert their roles in many ways for cardiac repair, remodeling and fibrosis (Figure 2).

Future directions

As mentioned above, there are different types of stem/progenitor cells in the heart tissue. However, their nature and clarification have not been well established. For example, are all types of stem/progenitor cells originated from one cell? In another word, one type of stem cells is responsible to produce all kinds of cells? Since lacking a specific marker for adult stem/progenitor cells, it is difficult to clarify the nature of stem/progenitor cells. The second issue is how important they are. If stem/progenitor cells could be depleted, are endothelial regeneration and heart remodeling restricted? To answer these questions, further investigation would be needed from basic study to clinic observation.

Currently, more than 200 clinical trials of cell therapy for cardiovascular disease have been conducted over past two decades, bone marrow derived MSCs are the most popular cells, while $CD34^+$ stem/progenitor cells and ADSCs are just minor components of cells applied in these clinical studies [6, 23]. Unfortunately, efficacy of stem cell therapy remains controversial. This is mainly because of the poor understanding of stem cells especially the resident stem/progenitor cells discussed above, there's even no common recognition of stem cell markers, not to

mention the isolation, purification, and expansion of cells to serve as clinical treatments in practice. Since stem cell therapy is still a promising strategy for heart regeneration, therefore, more endeavor and resources should be invested to investigate the different populations and distinct functions of stem cells in the heart.

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