This editorial refers to ‘Higher frequencies of BCRP⁺ cardiac resident cells in ischaemic human myocardium†, by M.Y. Emmert et al., on page 2830

It has been estimated that a serious myocardial infarction (MI) results in the loss of ~1 billion functional cardiomyocytes, which are replaced with a fibrous scar, frequently leading to heart failure. Experimental data demonstrate that the mitotic renewal in the human myocardium exists but at a very low rate: 1% annually at the age of 25 and 0.45% at the age of 75.¹ With this turnover rate, most cardiomyocytes will never be exchanged during a normal life span. Although the renewal rate may increase somewhat after injury, the heart itself is not able to effect large-scale cardiac regeneration. Thus, stem cell-based therapy may be a realistic strategy for providing a source of new functional cardiomyocytes. Additionally, stem cells may promote tissue healing through paracrine mechanisms. Regenerative stem cells may be derived from extracardiac sources as well as from the heart itself.

What do we know about cardiac resident progenitor cells?

Over the past decade, extensive studies have provided us with evidence that progenitor cells are present in the adult heart. In mice, cells expressing the stem cell factor receptor c-Kit,² stem cell antigen-1 (Sca-1),³ and transcription factor islet-1 (Isl-1),⁴ as well as side population (SP) cells⁵ have been identified as cardiac resident progenitor cells (CRPCs) due to their ability to differentiate into cardiomyocytes both in vivo and in vitro. Following the animal studies, a series of studies by several independent groups have suggested that CRPCs also exist in adult or postnatal hearts of humans (Figure 1),⁶⁻⁹ which are also identified by the expression of c-Kit, Sca-1, and Isl-1. In addition, cardiospheres cultured from human heart biopsies contain CRPCs and can proliferate in vitro (not addressed in Figure 1).¹⁰

The recent study by Emmert and colleagues demonstrates that the adult human heart contains a pool of SP cells expressing breast cancer resistance protein (BRCP).¹¹ Whereas BRCP⁺/CD31⁻ cells exhibit cardiac differentiation potential, BRCP⁺/CD31⁺ cells are endothelial cells (Figure 1).¹¹ SP cells were first identified in bone marrow by their ability to extrude the DNA-binding dye Hoechst 33342, which is mediated by the ATP-binding cassette transporter BRCP and MDR1. Human cardiac BRCP⁺ cells, similar to mouse cardiac SP cells, are negative for c-Kit.¹¹,¹² In the mouse heart, the greatest potential of cardiac SP cells for cardiomyogenic differentiation is also restricted to cells negative for CD31 but positive for Sca-1.¹³ However, Emmert and colleagues show that human cardiac BRCP⁺ cells are negative for Sca-1.

Although a Sca-1 epitope in human cells is disputed, data from van Vliet and colleagues indicate that Sca-1⁺ cells may be a unique population of CRPCs present in the fetal and adult human heart.⁶,⁹ Another population of CRPCs in the adult human heart are the c-Kit⁺ cells (Figure 1), which are also addressed by Emmert and colleagues.¹¹ They found that there were far fewer c-Kit⁺ cells (1000-fold) in the heart than their BCRP⁺ counterparts, and only in 30% of the samples were c-Kit⁺ cells detected. These data, to a certain extent, are not in line with previous studies showing that c-Kit⁺ cells are present as extensively as SP cells (MDR1⁺) in the adult human heart,⁶ and can be isolated from most patients and from all four heart chambers.⁷

What is the cardiac differentiation potential of human cardiac resident progenitor cells?

Sca-1⁺ cells isolated from the human heart are negative for CD45, CD34, CD133, and CD14, but positive for CD105, and express the early cardiac transcription factors GATA4 and Nkx2.5. Sca-1⁺ cells can be differentiated into beating and functional cardiomyocytes after stimulation with the demethylating agent 5-azacytidine (5-Aza; Figure 1).⁸,⁹ Additionally, Sca-1⁺ cells can also differentiate into endothelial and smooth muscle cells, indicating that they are multipotent cardiovascular progenitors.⁸,⁹ Emmert
et al. show that BCRP⁺ cells can differentiate into cells positive for cardiac troponin T (cTnT) after treatment with oxytocin in vitro. However, the cells do not have spontaneous beating activity. Further study is needed to investigate whether human BCRP⁺ cells, similar to Sca-1⁺ cells, can be expanded in vitro, and whether they are multipotent cardiovascular progenitors, and can develop into functional beating cardiomyocytes.

c-Kit⁺ cells are positive for GATA4 and Nkx2.5, but negative for Isl-1, CD45, and CD31, and can be differentiated into cTnI⁺ cells after 5-azacytidine treatment in vitro. However, no beating cardiomyocytes have been reported. In addition, they can differentiate into adipogenic and osteogenic cells, indicating their mesenchymal ancestry. c-Kit⁺ CRPCs are also able to give rise to cardiomyocytes, smooth muscle cells, and endothelial cells in patients with ischaemic heart failure. In the recently published phase I clinical ‘SCIPIO’ trial, Bolli et al. reported that intracoronary infusion of c-Kit⁺ CRPCs after bypass surgery in patients after MI resulted in improvement of ejection fraction. In 2004, Messina et al. reported generation of cardiospheres by cultivating cells isolated from adult human heart biopsies in suspension in vitro.
Cardiospheres contain a core of proliferating c-Kit+ cells (which also express Sca-1 and CD31), several layers of differentiating cells expressing cardiac and endothelial cell markers, and an outer layer composed of mesenchymal stromal cells. Cardiospheres are capable of long-term self-renewal, differentiating in vitro into electrically functional beating cardiomyocytes, and generating engraftment with cardiogenesis after intramyocardial delivery. However, cardiosphere-derived cells (CDCs) are phenotypically distinct from c-Kit+ ery. However, cardiosphere-derived cells (CDCs) are capable of long-term self-renewal, differentiating in vitro and establishing engraftment with cardiogenesis after intramyocardial delivery. However, cardiosphere-derived cells (CDCs) are phenotypically distinct from c-Kit+ cells identified in vivo. The phase I clinical CADUCEUS trial (http://clinicaltrials.gov/ct2/show/NCT00893360) investigates the safety of intracoronary infusion of CDCs in patients after MI.

Collectively, the data published so far suggest that a small pool of CRPCs is present in the adult human heart consisting of at least three different populations distinguished by expression of c-Kit, Sca-1, and BRCP.

**Where do cardiac resident progenitor cells come from?**

A number of questions remain to be answered before we can fully understand the potential role of CRPCs. Why do different CRPCs exist in the heart, and what are their likely origins? Adult CRPCs may be an extension of the progenitor cells in the embryonic heart. In this regard, Isl-1+ cardiac progenitor cells are found in the embryonic and postnatal mouse, rat, and human heart. Isl-1+ cells have been shown to identify the second heart field lineage cells and contribute to the development of the outflow tract, both atria, and the right ventricle. Additionally, Isl-1+, but c-Kit− cells are found in the cultured cells isolated from the adult human heart, although they are absent in the adult human heart in vivo. However, the Isl-1+ cells isolated from the postnatal heart do not extrude the Hoechst 33342 dye and do not express c-Kit and Sca-1, suggesting that Isl-1+ cells may not be the precursors of the CRPCs discussed above. Alternatively, is it possible that the CRPCs are from other tissues, e.g. bone marrow. Mouquet et al. reported that cardiac SP pools were decreased rapidly, as early as 1 day after MI in mice, and reconstituted to baseline levels within 7 days. The restoration of cardiac SP cells is accomplished by proliferation of resident cardiac SP cells and by homing of CD45+ bone marrow SP cells. After homing to the infarcted heart, the bone marrow SP cells undergo a phenotypic conversion evidenced by a loss of the expression of CD45.

**What does localization and quantification of cardiac resident progenitor cells in the adult heart tell us?**

Emmert et al. showed that BCRP+ cells are preferentially located in the right atria in the non-ischaemic heart (Figure 1).11 This observation matches the earlier findings that the right atrium is the best source of c-Kit+ cells.7 Sca-1+ cells are found within the atrium, the intra-atrial septum, and the atrium–ventricular boundary.8,9 It is attractive to speculate that the atria are the niche of different CRPCs, which are protected areas, exposed to low levels of haemodynamic stress. The atrial niche may have the ability to maintain CRPCs in an undifferentiated state. In the diseased heart, the CRPCs might be activated, proliferate, and migrate to the diseased area.

Interestingly, Emmert et al. observed a significantly increased number of both BCRP+/CD31− and BCRP+/CD31+ cells in the ischaemic ventricle (more precisely, the peri-infarct area of the ventricle) compared with the non-ischaemic ventricle, while the number of both cell types was not remarkably different in the right atria of both ischaemic and non-ischaemic patient groups.11 This, together with the finding that BCRP+CD31+ cells are able to differentiate into titin+ cardiomyocytes in the peri-infarct area, may suggest a potential role for BCRP+ cells in myocardial regeneration and neovascularization after cardiac injury.

In conclusion, there is accumulating evidence that at least three different populations of progenitor cells may be resident in the adult human heart. These cells represent a potentially attractive cell source for cardiac repair. However, their functional significance under physiological and pathological states has not been well defined. To understand fully the potential contribution of these cells to the repair of the damaged heart, further investigations are needed to elucidate their origins and to verify the ‘real resident progenitors. Additionally, limited knowledge exists regarding the molecular networks that regulate their proliferation, self-renewal, or differentiation states. Ongoing clinical trials may provide information on safety and efficacy of CRPCs in cardiac regeneration before we understand these important basal cell biology questions.

**Conflict of interest:** none declared.

**References**


