Plasticity and cardiovascular applications of multipotent adult progenitor cells

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SUMMARY

Cardiovascular disease is the leading cause of death worldwide, which has encouraged the search for new therapies that enable the treatment of patients in palliative and curative ways. In the past decade, the potential benefit of transplantation of cells that are able to substitute for the injured tissue has been studied with several cell populations, such as stem cells. Some of these cell populations, such as myoblasts and bone marrow cells, are already being used in clinical trials. The laboratory of CM Verfaillie has studied primitive progenitors, termed multipotent adult progenitor cells, which can be isolated from adult bone marrow. These cells can differentiate *in vitro* at the single-cell level into functional cells that belong to the three germ layers and contribute to most, if not all, somatic cell types after blastocyst injection. This remarkably broad differentiation potential makes this particular cell population a candidate for transplantation in tissues in need of regeneration. Here, we focus on the regenerative capacity of multipotent adult progenitor cells in several ischemic mouse models, such as acute and chronic myocardial infarction and limb ischemia.

KEYWORDS cardiovascular regeneration, ischemia, multipotent adult progenitor cells (MAPCs)

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INTRODUCTION

Every year in Europe and the US, approximately 550,000 people die of disease related to cardiac cell death.[1] The fundamental mechanism leading to the high morbidity and mortality in patients with any form of coronary artery disease is ischemia that induces myocardial injury and subsequent cardiomyocyte loss. Although the existence of cardiac progenitor cells has been reported and suggested to indicate a certain regeneration capacity,[2,3] adult myocardium—unlike skeletal muscle—does not show substantial regeneration after ischemic or other injury. Consequently, cardiomyocyte loss due to disease or injury is irreversible and typically results in the replacement of working cardiac tissue with nonfunctional scar tissue. Compensatory hypertrophy of the myocardium can, to a limited degree, alleviate the loss of contractile function that accompanies scar formation. Myocardial hypertrophy, however, predisposes the heart to arrhythmia, which frequently results in ventricular fibrillation and sudden death.[4,5]

EXISTING APPROACHES FOR CARDIAC REGENERATION

Currently, cardiac transplantation is the only curative therapeutic option for patients with severely diseased hearts. The ability to replace or regenerate damaged myocardium with functional, coupled cardiomyocytes would have obvious therapeutic value. To accomplish these effects, several approaches are actively being pursued by various research groups. Some work is focused on the *in vivo* manipulation of pre-existing cardiac cells, such as through inducing cardiomyocytes to reenter the cell cycle *in vivo*,[6] promoting cardiac cell migration and survival through the activation of antiapoptotic proteins (e.g. Akt),[7,8] and identifying genes that are able to initiate a cardiomyogenic differentiation, with the hope of being able to transdifferentiate cardiac fibroblasts into cardiomyocytes.[9]

Most groups are focused on the transplantation of new cells into a diseased heart, with the

hope that these cells will successfully contribute to host myocardial function. Several cell sources, including cells derived from tissues other than bone marrow (fetal cardiomyocytes, genetically modified skeletal myoblasts, and cardiomyocytes derived from embryonic stem cells [ESC]) and bone marrow-derived cells, have been successfully transplanted into normal hearts, diseased hearts, or both.[10]

LIMITATIONS OF CELL SOURCES OTHER THAN BONE MARROW

Fetal cardiomyocytes and embryonic stem cells

The cardiomyogenic potential of ESC from a variety of species, including humans, is well established. Indeed, fetal cardiomyocytes and ESC-derived cardiomyocytes stably engraft into and electromechanically couple with the myocardium of normal and injured adult mouse hearts.[11–13] The therapeutic use of these cells is, however, hindered by several ethical and technical caveats. The limited availability of fetal cardiomyocytes, the difficulty in obtaining pure ESC-derived cardiomyocytes without further genetic manipulation,[14] the consequent risk of teratoma formation,[15] and the immunogenicity of allogeneic cell grafts hamper the use of these cells for clinical purposes. Nuclear transfer has been proposed as an approach to obtain nonimmunogenic patient-matched ESC. Initial claims of success with human ESC had, however, to be withdrawn, which was an important setback for this area of study.[16] Other approaches, such as the induction of immunotolerance to a human ESC line by use of hematopoietic cells derived from it, are being explored. A prerequisite to these approaches is the ability to obtain efficient multilineage hematopoiesis from human ESC, which has not yet been fully accomplished.[17]

Skeletal myoblasts and satellite cells

Skeletal myoblasts are currently being tested as a source of cells for cardiac repair. Evidence from animal models suggests that implantation of skeletal myoblasts leads to an improvement in cardiac function. Long-term survival and electrical coupling of these cells within the myocardium, however, remain controversial. Paracrine mechanisms seem to be responsible, at least in part, for the beneficial effects of these myoblasts.[18] Clinical trials have been started in both Europe and the US. So far, they show improvement in most participants, although some cases of arrhythmia have been detected. This finding is due in part to a failed coupling between transplanted and host cells. The requirement of defibrillators in some patients has been a serious safety concern.[19]

THE CARDIOMYOGENIC POTENTIAL OF BONE MARROW-DERIVED CELL SOURCES

Several investigators have observed putative cardiomyogenesis from bone marrow-derived cells. For example, studies from the Fukuda laboratory have shown that 5-azacytidine treatment of bone marrow stromal cells, also called mesenchymal stem cells (MSC), gave rise to spontaneously contractile cells with some features consistent with cardiomyocytes.[20] Subsequent analysis indicated that these cells also expressed genes determining skeletal myogenic lineage, raising the possibility that the cells were partly differentiated skeletal myotubes.

Controversy has risen around the degree to which bone marrow cells can contribute to the formation of cardiomyocytes. The Anversa group has shown that transplantation of Lin^{-}/c-kit^{high} hematopoietic progenitors into mouse hearts immediately after coronary artery ligation gives rise to around 50% of the cells with cardiomyocyte, endothelial, and smooth muscle phenotypes, leading to improved cardiac function.[21] Subsequent studies from other groups have, however, indicated that, although improved function might occur following transplantation of Lin^{-}/c-kit^{high} or nonpurified bone marrow cells in cardiac infarcts, significantly less (<1%) cardiomyocyte differentiation was obtained.[22,23] Furthermore, the mechanism of lineage switch to cardiomyocytes (and vascular cells) is not clear. The *in vivo* contribution to cardiomyogenesis would probably be indirect through secretion of cytokines, as has been shown for MSC.[24]

Several reports have suggested that bone marrow stem cells possess a much greater degree of plasticity than previously believed.[25,26] In addition to the long-recognized hematopoietic, osteogenic, chondrogenic, and adipogenic potentials of bone marrow cells and stroma, bone marrow has been demonstrated to contain cells that form skeletal myocytes, hepatocytes, endothelium, smooth muscle, and neurons upon transplantation into adult recipients. Such unexpected plasticity could originate from a common precursor or from separate tissue-specific stem-like cells residing in the bone marrow. Apparent lineage commitment might also be due at least in part to fusion with host cells after transplantation.[27,28]

BONE MARROW PROGENITORS WITH CARDIOMYOGENIC POTENTIAL

Among the different populations of stem cells isolated, a population of primitive cells called multipotent adult progenitor cells (MAPCs) has attracted particular interest. These cells have multipotent differentiation and extensive proliferation potential at the single-cell level. Initially described by the Verfaillie group, MAPCs have been isolated from the bone marrow of a number of different types of mammals, including humans, nonhuman primate, swine, and rodents, and from other mammalian postnatal tissues.[29–33] After their initial description, other groups have also been able to isolate and characterize this rare population of stem cells.[34,35]

MAPCs are negative for CD44, CD45, major histocompatibility complex classes I and II, and c-kit and have low concentrations of Flk1. In mice, MAPCs also have low levels of Sca1 and SSEA-1. This phenotype has allowed these cells to be distinguished from other types of stem cells, such as hematopoietic stem cells or MSC. However, the lack of specific MAPC markers has raised questions about whether MAPCs would be an *in vitro* generated cell type without *in vivo* counterpart. We cannot yet completely answer to this question, but we have some evidence from profiling studies that MAPC are not merely a culture artifact. MSC derived under MAPC growth conditions could not be converted to an MAPC phenotype, and clonal isolation under identical culture conditions yielded clones with an MAPC signature and others with an MSC profile (CM Verfaillie, unpublished data). In addition, Anjos-Afonso and Bonnet[36] isolated SSEA-1 cells from bone marrow that closely resemble the MAPC phenotype without the need for a lengthy culture procedure. Finally, others have presented evidence for the existence of octamer-4 (Oct-4)-expressing cells in freshly isolated bone marrow.[37,38]

Human, swine, and rodent MAPCs can be expanded under defined culture conditions (2% fetal bovine serum, platelet-derived growth factor, epidermal growth factor, and leukemia inhibitory factor for rodents) without telomere shortening and express the ESC-specific transcription factors Oct-4 and Rex-1 (also known as zinc-finger protein 42, Zfp42), with a variable degree of Oct-4 expression among clones. When injected in an early blastocyst, one murine MAPC contributes to most, if not all, somatic cell types, and when transplanted in a nonirradiated host, murine MAPCs engraft and differentiate to the hematopoietic lineage and epithelium of liver, lung, and gut. Engraftment is increased when MAPCs are transplanted in a minimally irradiated host (CM Verfaillie *et al.,* unpublished data).[30]

The premise that MAPCs have the intrinsic capability to generate cardiomyocytes comes from blastocyst injection studies, in which up to 45% of the cardiac muscle has been derived from a single injected MAPC.[30] In addition, despite their multiple ESC-like characteristics, there is no evidence so far for teratoma formation after *in vivo* transplantation of MAPCs. We believe, therefore, that MAPCs capable of making cardiac and vascular cells could constitute a good source of donor cells for therapeutic cellular transplantation in the heart. We have examined the potential of MAPCs to contribute to cardiac regeneration in models of acute and chronic myocardial infarction (see below). A model of limb ischemia has also been developed for studying the therapeutic potential of MAPCs in peripheral vascular disease.

CARDIAC REGENERATION IN CHRONIC AND ACUTE CARDIAC ISCHEMIA

We have studied the effect of MAPC transplantation in a chronic model of myocardial infarction in rats. Although transplantation of MAPC was associated with reduced remodeling due to the increase in left ventricular volumes, stem cells did not improve the global pump function. The functional improvement detected could possibly be a consequence of favorable changes in the extracellular matrix composition, leading to some mechanical stabilization of the ventricular wall. Significant angiogenesis or arteriogenesis induction was not demonstrated in these studies, although some endothelial but not cardiomyocyte-differentiated cells were found at early time points.[39] We have previously shown the ability of MAPC to contribute to the cardiac tissue in the blastocyst, but the strict environment of chronically infarcted tissue could limit their survival. In addition, signaling clues might not be sufficient for directing MAPCs towards cardiac differentiation, which could be responsible for the absence of MAPC-derived cardiac cells.

Studies using models that sustain engraftment of MAPCs for a longer period, thus allowing assessment of their differentiation potential *in vivo*, are in progress. In our study, cell engraftment was observed for up to 2 weeks

after transplantation but 1 month after transplantation, MAPC could not be detected in the animals.[39] The low engraftment of the injected cells could be due to the fact that cells were injected 2 weeks after myocardial infarction, at the time when healing was still in the granulation phase. Also, the MAPC, which are negative for major histocompatibility complex I, were transplanted in animals that were not treated with an antibody to natural killer, so they might have been eliminated by natural killer cells.[40] Given these issues, further experiments are required in order to elucidate the potential of MAPCs in chronic cardiac ischemia.

We evaluated the long-term effect of *in situ* MAPC transplantation in acutely ischemic hearts (CM Verfaillie *et al.*, unpublished results). The effect of mouse MAPCs was compared with that for bone marrow cells. MAPC reduced the infarct size to a greater extent; induced a robust neovascularization response, supposedly through cytokine secretion in the ischemic heart; and durably improved the left ventricular function. Importantly, the establishment of a new microvascular network able to nourish with oxygen and nutrients the damaged tissue or areas at risk could rescue the cardiomyocytes from apoptosis and the consequent scar expansion. A clear correlation between the increase in vessel number and an improvement of cardiac function was found in our study, although a direct link between those two events remains to be proved.

VASCULAR DIFFERENTIATION *IN VITRO* AND *IN VIVO*

We have shown that MAPC differentiate into cells that express markers of endothelial cells and, most importantly, have proved that vascular endothelial growth factor induced MAPC to function like endothelial cells.[31,32] Physiologically, lipoproteins are modified by endothelial cells during transport in the artery wall, after which they maintain a permeability barrier through intercellular junctions that widen when exposed to hemodynamic forces or vasoactive agents, such as histamine. Moreover, endothelial cells release prothrombotic molecules such as von Willebrand factor, tissue factor, and plasminogen activator inhibitor to prevent bleeding and regulate leukocyte trafficking by changing expression levels of adhesion molecules in response to inflammation. Endothelium also reacts to hypoxia by producing vascular endothelial growth factor and expressing vascular endothelial growth factor receptors to increase vascular density. We demonstrated that endothelial cells generated from MAPCs can perform all these tasks when tested *in vitro* through measurement of von Willebrand factor release in response to histamine; acetylated LDL uptake; vascular tube formation when plated in matrigel substrate; upregulation of vascular endothelial growth factor, Flk1, and Tek in response to hypoxia; and upregulation of HLA in response to inflammatory cytokines, such as interleukin 1α.[31,32]

The *in vivo* potential of MAPCs as vascular progenitors is of particular interest. Initial studies conducted in a lung cancer tumor model in nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice demonstrated that human MAPCs transplanted into the mice contributed to up to 35% of the endothelial cells in the tumor vessels. This finding suggests the *in vivo* potential for vasculogenesis.[31] Furthermore, we found that MAPC-derived endothelial cells generated *in vitro* respond *in vivo* to angiogenic stimuli by participating in wound healing.[31] These findings together confirm that endothelial cells generated from MAPCs have all the functional characteristics of mature endothelium.

Other studies in our laboratory aimed to determine the vascular potential of MAPCs in comparison with other sources of stem cells with recognized potential for vascular differentiation, such as $AC133^+$ cells. MAPCs could be specified to both arterial and venous endothelia, whereas $AC133^+$ cells formed only venous endothelial cells under the same culture conditions (F Prosper *et al.*, unpublished data). This arterial endothelial cell potential, along with the capacity to differentiate into smooth muscle cells, could establish MAPCs as an attractive cell source for arteriogenesis. Indeed, one important feature that has not yet been addressed in the studies that claim a revascularization effect after stem cell injection in ischemic tissue is whether such process is due to arterial or venous endothelial differentiation. Revascularization should ideally induce arterial rather than venous growth, which would supply the oxygen required by the ischemic tissue.

DISCUSSION ON THE CARDIOVASCULAR REGENERATIVE POTENTIAL OF MAPC

We have previously shown that undifferentiated murine and human MAPC can differentiate into

endothelial cells and can directly contribute to blood vessels in tumors.[31] In the experiments performed in infarcted mice and rats, however, MAPCs did not survive in the heart microenvironment, probably because of an immune rejection against the marker protein LacZ or green fluorescent protein. We were, therefore, unable to assess whether they would have a similar capacity in this model. Nevertheless, we have preliminary data showing MAPC-derived endothelial cells at early time points after cell injection in acute infarcted immunosuppressed mice or chronic infarcted immunosuppressed rats. Moreover, we have evidence that MAPC contribute to endothelial cell populations in the ischemic limb of the mouse and significantly improve hindlimb function (CM Verfaillie *et al.*, unpublished data).

Importantly, we have demonstrated *in vitro* and *in vivo* the ability of MAPCs to specifically differentiate towards arterial or venous endothelium after specific cytokine treatment (F Prosper *et al.*, unpublished data). The ability to manipulate the cells in that manner could enable regeneration of the ischemic tissue and preservation of the area at risk by increasing oxygen supply.

The lack of *in vivo* cardiac muscle differentiation in ischemic hearts is perhaps surprising because we have shown that mouse MAPCs injected in the blastocyst can differentiate in cardiac muscle cells.[30] We have thus far, however, been unable to induce a (mature) cardiac phenotype in rodent MAPCs *in vitro*. Nevertheless, we have preliminary evidence that cardiac specification and commitment might be possible *in vitro* when apparently more-potent lines of rodent MAPCs are used.[41] Studies are in progress in which these MAPC lines in their undifferentiated state and following cardiac commitment are being grafted in a mouse model of acute myocardial infarction.

CONCLUSIONS

Taking all these data together, we have demonstrated that MAPCs can functionally improve the heart or limb muscle after an ischemic insult in rodents. This result was not due only to an indirect paracrine effect on neovascularization but also through the contribution of MAPC to vessels. Very importantly, MAPC can be directed towards a specific arterial endothelial cell phenotype, a manipulation that could further improve and optimize strategies for vascular regeneration in ischemic patients and might also have implications for the design of endothelial cell-coated artificial arterial grafts.

Although additional studies are required to prove their *in vivo* cardiomyogenic potential, we now have promising evidence for cardiomyocyte specification *in vitro* after specific sequential cytokine treatment of new, more potent MAPC clones. On the basis of the encouraging results in rodents, it will be interesting to determine whether this effect is also apparent in larger animal models and, ultimately, in patients with cardiac or limb ischemia.

KEY POINTS

- Many embryonic and adult cell sources have been tested for their *in vivo* cardiomyogenic potential
- The extent to which bone marrow cells differentiate to cardiomyocytes in the ischemic heart is still controversial
- Multipotent adult progenitor cells comprise a bone marrow-derived adult stem cell population with multilineage differentiation capacity *in vivo* and *in vitro*
- Acute and chronic cardiac ischemic hearts functionally improve after multipotent adult progenitor cell transplantation in rodent models
- Multipotent adult progenitor cells can differentiate *in vitro* and *in vivo* into functional endothelial cells and contribute to vascular regeneration in mice with ischemic hearts or limbs

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Competing interests

The authors declared they have no competing interests.

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