Stem Cells and Cardiovascular and Renal Disease: Today and Tomorrow

Volker Schächinger and Andreas M. Zeiher

J.W. Goethe University, Frankfurt, Germany

The traditional view that organs have only limited regenerative capacity has been challenged in recent years as adult bone marrow stem cells as well as circulating progenitor cells have been identified to retain the plasticity to participate in neovascularization, a process so far believed not to be possible after birth. An organ that is damaged by ischemia causes the release of cytokines; these act via the flowing blood and stimulate the bone marrow, which then mobilizes progenitor cells to the blood and directs them to adhere to and migrate into the damaged organ. Thus, these progenitor cells most likely constitute a natural repair mechanism that counteracts degenerative or aging processes. On the basis of encouraging experimental data, first clinical trials have been established to demonstrate the safety and the feasibility of progenitor cell therapy in case of peripheral artery disease or myocardial infarction. Trials investigating injection of bone marrow or circulating progenitor cells into the coronary artery after an acute myocardial infarction not only demonstrates safety of the procedure but also gave hints toward efficacy. Nevertheless, these findings have to be validated by subsequent larger, prospective, randomized, controlled trials. There are also potential topics in nephrology, where modification of progenitor cell activity might be of benefit, such as renal ischemic disease, glomerular disease, and renal transplant vasculopathy. Finding a way to integrate the principle of progenitor cell action into therapeutic efforts might provide a completely new therapeutic strategy that not only attempts to retard disease progression but furthermore targets to regenerate damaged organs.


Until recently, it was thought that the heart does not possess a regenerative capacity, because adult cardiomyocytes are terminally differentiated and have lost their capacity to renew. The only response to an increased functional demand was seen to be hypertrophy of cardiomyocytes. However, this view has been challenged by findings in patients after heart transplantation with a sex-mismatch transplantation (1,2): In myocardial biopsies of male recipient patients who received a female donor heart, Y chromosomes were found, indicating that recipient cells were coming from outside the donor heart, migrating, and integrating into the transplanted heart. Those Y chromosomes containing cells were identified as both cardiomyocytes as vascular cells (e.g., endothelium).

There is evidence that the cells regenerating the heart are coming from the bone marrow as demonstrated in sex-mismatch bone marrow transplant patients who undergo a myocardiobiosis (3). Similar findings have been obtained for the kidneys. Poulsom et al. (4) found Y chromosomes in renal tubules and glomeruli in female mice that received a male bone marrow transplant. Before these findings, Asahara et al. (5) already identified progenitor cells with an endothelial phenotype (endothelial progenitor cells) circulating in the blood. It is interesting that the amount of peripheral endothelial progenitor cells is reduced with increasing number of cardiovascular risk factors (6), and, in contrast, increased colony-forming capacity of endothelial progenitor cells is associated with improved endothelial vasodilator function (7), an index of vascular integrity that predicts a favorable cardiovascular prognosis (8).

Recent evidence indicates that the plasticity of adult stem or progenitor cells (more differentiated stem cells) that are released from the bone marrow is much larger than previously suspected (9,10). Traditionally, it has been thought that stem cells are committed to certain cell lines (tissue specificity) and, with increasing degree of maturation, lose their ability to dedifferentiate (return to a more immature form) or to transdifferentiate (changing the path to another cell line).

Physiologic Role of Progenitor Cells

It is intriguing to speculate that progenitor cells that circulate in the blood may be part of a physiologic repair system designed by nature to repair damaged organs (11). However, this regenerative mechanism is most likely adjusted to a low-grade and slow injury, probably as a counterweight for degenerative or aging processes. However, in case of a “mass destruction,” such as an acute myocardial infarction, the physiologic repair capacity is obviously by no way sufficient.

However, ischemia is a trigger for the release of progenitor cells from the bone marrow, leading to the release of messenger molecules (growth factors, cytokines) that circulate in the blood, perfusing also the bone marrow (e.g., erythropoietin or granulocyte colony-stimulating factor) (12). These stimuli take part in cleavage and mobilization of progenitor cells from the bone marrow, entering the blood pool. When passing ischemic tissue, these progenitor cells are extracted and targeted to ad-
here and migrate by the receptors and messenger proteins released from the ischemic tissue, thereby also taking part in neovascularization.

Indeed, it has been shown experimentally for the heart (13–16) as well as for the kidney (17) that progenitor cells from the bone marrow (genetically marked for the possibility to stain for histology) integrate after an ischemic injury (Figure 1). In line, these studies demonstrated that animals that were treated with progenitor cells experienced a functional improvement in organ function such as reduced left ventricular (LV) remodeling and improved LV function in the case of the heart (14) or reduced urea increase after renal artery ligation in the case of the kidney (17).

However, despite the finding that bone marrow cells transdifferentiate into premature parenchymatous or vascular (endothelial) cells or fuse with mature cells, there is an ongoing debate about the extent and the importance of these observations (18–20). Other potential therapeutic effects of progenitor cells include production of cytokines such as vascular endothelial growth factor, stromal cell derived factor 1 (SDF-1), hepatocyte growth factor, or IGF-1 (21). Thus, therapy with progenitor cells might amplify biochemical signaling cascades that contribute to regeneration of organs, especially by neovascularization.

The regenerative capacity of progenitor cells might be used therapeutically if it is possible to intensify the effect. Indeed, experimental studies in acute myocardial infarction, renal ischemia, and hindlimb ischemia indicate that external application of progenitor cells is a suitable strategy to improve ischemia and rescue organ function (13–17).

**Clinical Studies**

Various cell types have been approached to use to regenerate the heart: skeletal myoblasts, cultivated after skeletal muscle biopsy (22–26), and bone marrow cells or circulating progenitor cells (27–29). Whereas skeletal myoblasts seem to be limited to differentiate into cardiomyocytes, bone marrow or circulating progenitor cells may have a larger therapeutic potential, including paracrine actions. Bone marrow cells have also been used in patients with peripheral artery disease (Therapeutic Angiogenesis using Cell Transplantation Study) (30). In addition, serious life-threatening ventricular arrhythmias have been observed in patients who received a cardiac application of skeletal myoblasts (22), which is not reported in patients who received bone marrow (27–30) or circulating progenitor cells (28).

**Acute Myocardial Infarction**

In a first clinical trial, Strauer et al. (29) treated 10 patients after an acute myocardial infarction by injecting progenitor cells that were aspirated from the bone marrow into the infarct coronary artery. A positive effect on myocardial perfusion as well as LV function was seen. Another pilot trial delivered a selected fraction of bone marrow cells (CD 133+ cells) to the heart by intramuscular injection during surgery (32).

In the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial, finally 59 patients were investigated 3 to 7 d after successful percutaneous revascularization via stent implantation of an infarct artery during acute myocardial infarction (27,28). Patients were treated with either bone marrow–derived progenitor cells or circulating progenitor cells that were given during low-pressure balloon insufflation directly into the lumen of the infarct artery. The study demonstrated that intracoronary infusion of progenitor cells with both types of cells was safe and feasible, because there were no unexpected adverse events and no evidence of inflammation or microembolization induced by the cell therapy. In addition, improvement of LV ejection fraction was seen associated with improved viability measured by positron emission tomography (27) and reduction of infarct size, assessed by magnetic resonance imaging (late enhancement) (33). In addition, coronary flow reserve improved significantly into the infarct artery up to the level of the reference artery, giving a hint that probably neovascularization and, therefore, increases in vascular conductance capacity might be associated with progenitor cell therapy.

These encouraging results were confirmed by the recently presented Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial (34), which randomized 60 patients 1:1 with a control group to intracoronary bone marrow–derived progenitor cell therapy after acute myocardial infarction. Whereas LV ejection fraction improved by 6.7% in the bone marrow–treated group, there was only a marginal change of LV ejection fraction of 0.7% in the control group, which demonstrated a significant difference in favor of progenitor cell therapy. Further studies will have to establish formally this novel therapy and define definitely the value within the current clinical scenario.

**Chronic Ischemic Cardiomyopathy**

In a chronic stage of ischemic heart disease, the prerequisites for a successful progenitor cell therapy are probably less favor-
able than after an acute myocardial infarction. During acute myocardial infarction, an acutely injured ischemic myocardium is sensitized for the reception of progenitor cells, because the endothelium is activated, expresses receptors, and releases messenger molecules that target adherence and migration of progenitor cells.

To overcome the lack of an incentive of progenitor cells to migrate to the chronically damaged heart, some studies have tried to inject bone marrow–derived progenitor cells directly into the heart muscle via percutaneous techniques or by surgery. Limited by usually a small patient number, these studies so far indicate the safety and the feasibility of this kind of treatment as well as give a hint toward efficiency, because some patients improved their ejection fraction (35–37).

A recent preliminary report of the MAGIC cell study (38) suggested that this kind of therapy might be associated with increased restenosis rate. However, because of various limitations of this study (incompletely reported small sample size, heterogeneous patient population, delayed revascularization after acute infarction), the conclusions drawn from that study are limited. In contrast, other studies using progenitor cells alone (e.g., BOOST, TOPCARE-AMI) do not indicate an increased restenosis rate.

Perspectives
The use of stem or progenitor cells to treat or restore the function of damaged organs such as the heart or the kidney is a completely new therapeutic concept. In contrast to all previously existing medical treatment strategies, progenitor cell therapy does not only target to halt progression of the disease but furthermore offers the perspective to actually regenerate the function. However, under discussion are various topics that have to be resolved:

1. The mechanism of action of progenitor cells is not fully understood. It might include paracrine activity of the cells, neovascularization, and, probably, transdifferentiation or fusion. The relative importance of these various mechanisms has to be determined. In addition, other mechanisms that are yet unknown might be involved.

2. It might be necessary to optimize progenitor cell therapy, by enhancing mobilization and/or by enhancing homing of the cells. However, strategies that improve mobilization (e.g., granulocyte colony-stimulating factor) modify molecular targets in a way that mobilizes cells on the one hand but also impairs their functional capacity to migrate and adhere on the other hand. Therefore, probably different strategies have to be found.

3. The concept of cell therapy has to be more refined. There is currently still no consensus on the combination of cells or how to identify the subtype of cells that gives the best approach to reach the therapeutic goal. That is, the markers used so far to identify progenitor cells (e.g., CD34+ or the more immature marker CD133+) are not linked directly to the progenitor activity of the cell. In addition, therapeutic methods to improve progenitor cell function (e.g., gene therapy) might be useful in the future. In addition, the best way to apply cells (number, route of application) has not yet been defined.

Nevertheless, progenitor cell therapy gives new opportunities for treatment of damaged organs. Clinical studies are currently ongoing in patients with coronary artery disease, such as the multicenter, double-blind, controlled Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction trial comparing intracoronary infusion of bone marrow progenitor cells versus placebo in 200 patients after myocardial infarction. However, administration of progenitor cells has not been limited to actual application of cells; other strategies might involve enhancement of regenerative capacities of organ-specific resident progenitor cells (demonstrated in the heart, currently only suspected in the kidney) by pharmaceutical strategies. Indeed, statins, which are known to improve cardiovascular prognosis, have been demonstrated to increase the number of circulating progenitor cells (38) and, of interest, increase the number of circulating progenitor cells incorporated into the neointima after vascular damage, thereby counteracting the restenotic process (40,41).

There are also several potential fields of interest in nephrology, such as ischemic renal disease (17), regeneration of glomeruli, or tubular disease (42) or transplant vascular disease by modifying reendothelialization with progenitor cells or reducing smooth muscle proliferation and, thereby counteracting transplant vasculopathy (43).

References
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