

# Cardiac and renal cell therapies: similarities and differences

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**Patients with terminal cardiac or renal disease have few therapeutic options besides organ transplantation. Optimally, cell therapies would be used both in acute and chronic stages of such diseases. In the injured myocardium, the main therapeutic goal is reestablishment of adequate perfusion and cardiac output. This can be achieved by stem cell (SC) infusions, and currently several clinical trials have provided promising results. Considering the heart's low intrinsic capacity for regeneration and its paucity of resident cardiac SCs, we believe that induction of angiogenesis must be the primary goal, thereby promoting activation of resident SCs as well as mobilization of perivascular mesenchymal SCs that can mediate myocardial regeneration. Renal tissue, in contrast to the myocardium, has a high intrinsic capacity to respond to injuries and thus repair itself. Infusion of bone marrow (BM) cells or of their sub-populations protects the injured renal tissue and elicits immediate activation and proliferation of resident cells, which are able to undertake repair and regeneration of structures of both mesenchymal and epithelial origin. Experimental evidence indicates that infused cells function essentially through paracrine pathways, decreasing inflammation and fibrosis. In both severe cardiac and renal disorders, cell therapies appear to be a promising therapeutic option.**

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Cardiovascular diseases are the leading cause of morbidity and mortality throughout the world. Despite significant progress in cardiovascular medicine, mortality rates have remained steady during the past decade. Similarly, the number of patients developing end-stage renal disease is steadily increasing. In both groups of diseases, transplantation of the organ is frequently the only therapeutic option, which is, however, hampered because of the limited availability of donors and the complications associated with allogeneic transplantation. Cell therapies have been proposed in both scenarios as a promising alternative therapy and, at least in cardiovascular diseases, numerous experimental studies and clinical trials have provided promising results. Although we are still far from understanding all of the mechanisms involved, most scientists would agree that in cardiology there is no longer a question of whether cell therapies should be used in patients, but rather how they should be used.<sup>1</sup>

In the repair of both acute cardiac ischemic lesions and their late consequences, such as remodeling and fibrosis leading to terminal myocardial insufficiency, two main goals are being pursued: (1) revascularization of the ischemic heart tissue, and (2) reestablishment of normal myocardial contractility. As virtually every cardiomyocyte requires a physical contact with a blood capillary, the two goals are closely related. In addition, the collective contractile work of cardiomyocytes must be coordinated, which requires electric coupling of individual cardiomyocytes.

Pioneering studies on cardiac cell therapies have used implants of skeletal muscle cell progenitors for the reestablishment of cardiac contractility.<sup>2</sup> Although this has been partly achieved, and the feasibility of cell therapy of the injured myocardium has been demonstrated, incomplete coordination of cell contraction and occasional ventricular fibrillation have raised safety concerns. Subsequent studies have mainly used bone marrow (BM)-derived cells, either the whole mononuclear fraction or selected cell sub-populations.<sup>3</sup> The overall impression is that most clinical studies, some of which include large numbers of controls, have reported benefits to patients, often with a significant long-term improvement of their clinical state.<sup>4</sup>

Studies with sex-mismatched heart or BM transplants have shown some evidence of a potential direct participation of BM-derived cells in the generation of new cardiomyocytes.<sup>5</sup> However, the reported numbers of differentiated

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and engrafted stem cells (SCs) are very low and insufficient to explain the observed clinical improvements. One of the proposed mechanisms for neo-cardiomyogenesis has been the fusion of implanted cells with resident cardiac cells; however, this hypothesis has not received further experimental support.

Two mechanisms of the observed long-term improvement of heart function after cell therapy have been proposed, potentially functioning together: cardiomyogenesis and angiogenesis. Despite the fact that the spontaneous regeneration capacity of the myocardium is quite low, it has been convincingly shown that resident heart SCs are present within the myocardium, and that they can participate in heart regeneration.<sup>6</sup> An additional type of SC was subsequently identified, dwelling in the pericardium. In embryogenesis, the coronary vasculature derives from the pericardium, and these pericardial cells are thought to support the regeneration of both cardiac blood vessels and cardiomyocytes.<sup>7</sup> To boost the physiologically low capacity of cardiac regeneration, effective cell therapies should provide either an increased number of SCs or the additional stimuli to promote intrinsic SC activation and proliferation, together resulting in efficient heart regeneration after an acute infarct and in secondary chronic heart failure.

The number of SCs that do differentiate into cardiomyocytes after injection is rather low. However, the observed beneficial effects can be quite longstanding. In our experience, improvement of heart function was still observed after 12 months post-therapy for severe heart failure,<sup>8</sup> and in a recent 5-year follow-up of the group all patients were still well. From this follows the fact that the introduced cells must elicit a long-term regeneration process, which may work by stimulating resident cell progenitors. The required stimuli may be derived from implanted BM-derived cells, which have been shown to produce a broad set of cytokines that stimulate SC proliferation, commitment, and differentiation. They could function through paracrine pathways. Currently, this mechanism of myocardium repair is considered a plausible explanation for the favorable outcome of cardiac cell therapies.<sup>9</sup>

Alternatively, angiogenesis may be intimately involved in cardiomyogenesis by facilitating myocardial regeneration. Data on sustained angiogenesis were reported in a histological study of heart tissue from a patient who died from unrelated causes 11 months after transendocardial cell therapy.<sup>10</sup> Intense and late angiogenesis in fibrotic cicatricial areas was associated with decreased density of collagen matrix and with proliferation and hyperplasia of pericytes. Moreover, these cells were shown to express myocardial cytoskeleton markers while still located within the blood vessel walls, and even more so after migrating from the vessel wall into the adjacent myocardium, which was rich in very small cardiomyocytes, suggestive of neo-cardiomyogenesis. Both requirements for effective clinical heart therapy were thus met: angiogenesis and cardiomyogenesis. The increasing evidence showing that perivascular pericytes have properties

of mesenchymal stem cells (mSCs) is consistent with this hypothesis.<sup>11</sup> Generation of endothelial cells, pericytes, vascular smooth muscle cells, and other muscle cell progenitors are intrinsic properties of mSCs. When blood vessel stabilization is carried out by pericytes, angiogenesis is a self-sustained and continued process.<sup>12</sup> The hypothesis that the long-term regeneration of heart tissue is mediated by local mesenchymal cells, potentially associated with mobilization of resident cardiac progenitors, may thus explain, at least in part, the observed clinical results.

The major cell lineages relevant for cardiac repair, namely blood vessel cells and cardiomyocytes, belong to the same mesenchymal cell family and may originate from common SCs. These cells are present in the BM mononuclear fraction and can undergo long-term proliferation and differentiation. In contrast, renal tissue contains differentiated cells of diverse embryonic origins, with complex structures associated with blood vessels and connective tissue. To sustain proper renal function, these cells must maintain their functional relationship and the spatial order. Another major difference is the fact that renal tissue is quite efficient in spontaneous repair of less severe acute lesions.

Similar to cardiac tissue, sex-mismatched kidney transplants have also shown rare tubular epithelial cells of BM origin, suggesting the possibility of transdifferentiation.<sup>13</sup> As in cardiac repair, very low level of fusion of administered precursor cells with target cells in the kidney, potentially contributing to organ repair, has also been reported. Thus, indirect effects of cell therapies have to be considered, and specific nephronal segments that show engraftment of exogenous cells need to be further examined.

Since 2001, several protocols of BM cell infusion in diverse models of kidney injury have shown that BM stem/progenitor cells can differentiate into various renal cells, particularly those of mesenchymal or vascular origin, including mesangial cells, and glomerular or peritubular endothelial cells.<sup>14</sup> Moreover, differentiation of administered cells into tubular epithelial cells and podocytes was reported, independently of the type of BM cell fraction or kidney injury.<sup>15</sup> Similar to myocardial regeneration, further studies have proposed that BM cells function mainly on the intra-renal pool of SCs. The kidney contains, as has been reported, numerous resident SCs localized at several sites: in the renal papilla, among tubular epithelial cells, Bowman's capsule, and medullary vascular bundles.<sup>16</sup> Nestin, a multi-lineage marker, has been proposed to label progenitor cells and to help with the identification of this cell population in the kidney. Nestin-expressing cells were localized in the renal papilla and along the vasa recta in the medulla under normal conditions, but they migrated, following ischemic injury, from the papilla/medulla to the cortex.<sup>17</sup> This finding is consistent with studies that demonstrated that renal SCs enter the cell cycle during self-repair following ischemic injury, and quickly 'disappear' from the papilla because of out-migration and not caused by their apoptosis.

In principle, mSCs can directly differentiate into cells of the same lineage, that is, glomerular mesangial or blood vessel cells. However, several models have shown that their participation in renal regeneration was only indirect, with a considerable improvement of renal function in several models of injury. After injection of a lineage-negative BM cell fraction that contains mSCs, or purified mSCs,<sup>18</sup> their beneficial effects were mediated by increased tubular cell proliferation, decrease in tubular apoptosis, anti-inflammatory effects, and angiogenic stimuli.

Paracrine factors secreted by mSCs might explain their beneficial effects in acute kidney injury. These enhance endothelial cell proliferation and differentiation. When mSCs were infused just before ischemia/reperfusion injury, these cells quickly homed to the renal microvascular circulation, and led to decreased endogenous cell apoptosis in regions that contained mSCs.<sup>16</sup>

Our group has recently demonstrated that the infusion of BM mononuclear cells had a renoprotective effect in unilateral ureteral obstruction in animals. After 14 days of obstruction, these animals showed an enhancement of tubular proliferation, decrease in tubular cells apoptosis, and mobilization of nestin-positive cells into the interstitial and peritubular spaces, without major incorporation of the labeled donor cells into recipient renal tissue.

One of the major concerns in cell therapies that use mesenchymal progenitors is a potential increase of fibrosis mediated by infiltrating myofibroblasts, as it has been suggested that one of the possible origins of myofibroblasts is the BM. This was concluded from several experiments that demonstrated that myofibroblasts and fibroblasts were thought to originate from BM cells after their transplantation, as well as from renal resident stem/progenitor cells.<sup>19</sup> Although conversion of nestin-positive cells into myofibroblasts has been reported, we observed a decrease in both myofibroblasts and the degree of fibrosis. An increase in peritubular capillaries with some nestin-positive cells was observed, suggesting an increased angiogenesis. Similar to the cardiac fibrotic tissue, in which we observed a decreased density of collagen after cell therapy, the augmented angiogenesis may be associated with a decrease in fibrosis, likely mediated by activation of metalloproteinases that are associated with blood vessel growth.

Another concern is associated with the use of other sources of mSCs, notably those derived from adipose tissue. As cells infused into the kidney localize mainly in glomeruli, local concentration of such cells can be relatively high. Bone marrow cell suspensions contain different cells that may survive for a time, and eventually engraft into glomeruli, thereby participating in matrix production. As adipose tissue-derived mesenchymal cells are infused as a pure cell population, their intrinsic tendency to differentiate into adipocytes when administered in high numbers can occur in glomeruli.<sup>20</sup> Such therapeutic protocols should obviously be used with caution.

In conclusion, SC therapies can be beneficial in renal as well as in cardiac disorders. Despite differences in structure,

embryonic origin, and function, the introduction of BM mononuclear cells, potentially enriched in mSCs, seems to stimulate resident stem cells and other cells in both organs to react to cell injury and inflammation. This action promotes both ordered organ protection and regeneration after injury. In the kidney, the major cytoprotective effect was mediated by decreased apoptosis, followed by an intense mobilization of resident nestin-positive progenitors and active regeneration of tubular structures. Increased angiogenesis appeared to be an important effect, as well as decreased fibrosis and inflammation. In the myocardium, where resident cardiac SCs are a relatively minor population, and where the microvascular density of the coronary circulation is normally very high, we believe that angiogenesis is the primary and major regenerative event, followed by the *in situ* increase of perivascular mSCs that are required for neo-cardiomyogenesis.

Although cellular and molecular mechanisms involved have to be better understood, well-designed experimental and clinical protocols with mSCs or other progenitor cells are expected to shed more light on their therapeutic capacity in patients with severe renal lesions. Despite technical limitations and ethical concerns, SC therapy seems to provide the hope of patient-specific renal repair in diseases in which currently available therapies remain essentially ineffective.

#### DISCLOSURE

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