Editorial

Cardiac differentiation of mesenchymal stem cells in sex mis-matched transplanted hearts: self-repair or just a visit?

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See article by Bayes-Genis et al. [10] (pages 404–410) in this issue.

Currently, a paradigm shift from the widely accepted dogma of the heart being incapable of self-repair is occurring. This is mostly owing to recent revolutionary observations that host-derived stem cells, presumably mesenchymal stem cells derived from the bone marrow, can be recruited to, engraft within the myocardium and may participate in the regeneration of heart function [1–3]. The apparent plasticity of adult stem cells has prompted the possibility that bone marrow-derived mesenchymal cells could be isolated from patients, sub-cultivated in vitro and reintroduced after occurrence of heart disease. Bone marrow cells and cardiomyocytes are both arising from the early mesoderm. However, the cardiomyocyte progenitors are developed from the lateral plate mesoderm under the inducing influence of differentiation factors secreted by the adjacent endoderm, whereas the bone marrow is derived from the somitic dorsal mesoderm. Despite these differences in origin, several studies performed on rodents [3–6], pigs [7] as well as on humans [8,9] have conclusively demonstrated that mesenchymal stem cells own the potency to differentiate to a cardiomyocyte phenotype in the adult heart. With the study of Bayes-Genis et al. in this issue [10], further evidence is provided that stem cells, presumably mesenchymal stem cells derived from the bone marrow, respond to cardiac tissue signals with differentiation towards the cardiac lineage and integration in the cardiac tissue microarchitecture. In the study of Bayes-Genis et al. cardiomyocytes originating from recipients of transplanted hearts were found in sex-mismatch cardiac allografts. Sex-mismatched cardiac transplantation, i.e., cases in which male patients receive hearts from female donors and vice versa, provide the opportunity to investigate whether stem cells or tissue-specific precursor cells translocate from the recipient to the graft. Cell migration from the allograft to the recipient results in systemic chimerism, whereas cell migration from the host to the transplanted organ results in chimerism of the organ [11]. Allografted female hearts into human male recipients are commonly analyzed for cardiac chimerism by determining Y chromosome-positive cells from the recipient present in the donor heart. The investigation of cardiac chimerism is elegantly performed by fluorescence in situ hybridization using Y chromosome-specific hybridization probes correlated with immunohistochemistry of cardiac specific markers.

The degree of cardiac chimerism is currently a matter of intensive discussion [12]. Bayes-Genis et al. found 1–2% mature cardiomyocytes from the host in biopsy specimen. This observation is in line with most previous studies which demonstrated that cardiomyocyte chimerism within an allografted human heart occurs at very low levels, i.e., 0.02–1% [13,14]. Only the study of Quiani et al. [11] reported that approximately 30% of transplanted myocardium is regenerated within 4 to 28 days after allotransplantation by stem cell-derived cardiomyocytes originating from the recipient. Several reasons may account for the observed differences: human cardiac allografts are infiltrated with a population of host-derived leukocytes, i.e., macrophages and T lymphocytes within hours of engraftment, which, naturally, results in the occurrence of Y chromosomes in the transplanted female cardiac tissue. Y chromosome-positive cardiac cells could have arisen from the small amount of host atrial myocardium typically retained after cardiac transplantation. A further point that should not be underestimated is the possibility of fetal microchimerism, which means that fetal cells pass into the maternal circulation and can survive in the mother for many years or even a whole life [15]. Consequently, Y-chromosome-positive cells may originate from male
stem cells transferred as a result of fetal–maternal transfusion during pregnancy. To address this issue, Bayes-Genis et al. performed their study on male patients who received hearts from female donors as well as female patients who received an allograft from a male donor. Under the latter conditions fetal microchimerism is not possible. Furthermore, the cardiac tissue was rigorously screened for recipient cells morphologically recognizable as infiltrating lymphocytes and macrophages.

The study of Bayes-Genis et al. surpasses previous studies on cardiac chimerism regarding the investigation of transplanted hearts from the same patients for cardiac chimerism 4 months and 12 months after transplantation. It was found that the number of recipient cells in the heart tissue was reduced by approximately 40% after 12 months as compared to hearts 4 months after transplantation, corroborating the results of a previous study that demonstrated a higher percentage of recipient-derived cardiomyocytes at early stages after transplantation [11]. This decline in chimerism may be related to the process of early acute allograft rejection, suggesting that chimerism requires an injury event. All the cardiac tissues analyzed in the study of Bayes-Genis et al. had been obtained from patients who suffered from rejection episodes which may suggest that a scarcely defined microenvironment of inflammation may be a prerequisite for cardiac chimerism. However, although it sounds reasonable that cell death, inflammatory infiltrates and released cytokines may act as molecular signals for the chemotraction and activation of stem cells, the tissue microenvironment necessary to induce tissue-specific differentiation of stem cells is currently completely unknown.

Most studies on cardiac chimerism, including the work of Bayes-Genis et al., discuss that the recipient-derived cardiac cells in the transplanted heart are the progeny of stem cells or progenitor cells of mesenchymal stem cells originating in the bone marrow. However, it should be stressed that the origin and fate of recipient cells in the transplanted human heart have not yet been unraveled beyond controversy, although recent experimental success with repair of infarcted myocardium by bone marrow-derived cells strongly suggests that the cells colonizing the new heart are mesenchymal stem cells mobilized from the bone marrow following a so far unknown stimulus.

The physiological function of cardiac chimerism remains obscure. Whereas transplanted bone marrow-derived stem cells have been demonstrated to restore function of the infarcted heart, no data exist as to whether chimeric recipient cells can improve performance of the transplanted heart which may, however, be related to a lack in sensitivity of transthoracic echocardiography that was used to assess heart function. The extremely low number of recipient-derived cardiomyocytes observed in transplanted hearts suggests that these cells are just visitors, unable to meet a long-term demand for organ repair. It should, however, be kept in mind that the job to be done by recipient-derived cardiomyocytes is currently completely unknown. We therefore cannot exclude that recipient-derived cardiomyocytes in allografted hearts—despite their low number—play a sophisticated role in tissue repair — and that they pass away years after successful transplantation, having fulfilled their assigned task.

**References**


