Stem cell transplantation and cardiac regeneration after myocardial infarction in SCID mice: Human MAPCs are effective and safe

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Introduction:

Clinical studies suggest that transplantation of total bone marrow (BM) after myocardial infarction (MI) is feasible and potentially effective. However, focusing on a defined BM-derived stem cell type may enable a more specific and optimized treatment. Multilineage differentiation potential makes BM-derived multipotent adult progenitor cells (MAPCs) a promising stem cell pool for regenerative purposes. We analyzed the cardioregenerative potential of human MAPCs in a murine model of myocardial infarction.

Materials and Methods:

Human MAPCs were selected by negative depletion of CD45+/Glycophorin+ BM cells and plated on fibronectin coated dishes. In vitro, stem cells were analyzed by RT-PCR. In vivo, we transplanted hMAPCs (5x10^5) by intramyocardial injection after MI in immunodeficient SCID beige mice. 6 and 30 days after the surgical procedure, pressure volume relationships were investigated in vivo. Heart tissues were analyzed immunohistochemically.

Results:

RT-PCR experiments on early hMAPCs passages evidenced an expression of Oct 4, a stem cell marker indicating pluripotency. In later passages, cardiac markers (Nkx2.5, GATA4, MLC-2v, MLC-2a, ANP, TnT, TnI, Cx 43) and smooth muscle cell markers (SMA, SM22α) were expressed. Transplantation of hMAPC into the ischemic border zone after MI resulted in an improved cardiac function at day 6 (EF 26 vs. 20%) and day 30 (EF 30 vs. 23%). Co-localisation of hMAPC marker vimentin and SMA in immunohistochemistry demonstrated that hMAPCs integrate into vessels in the peri-infarct region and show smooth-muscle-like characteristics. Furthermore, engrafted hMAPCs formed cardiomyocyte-like cells expressing cardiac proteins Nkx 2.5 and MHC. The proliferation marker Ki67 was absent in immunohistochemistry, and teratoma formation was not found indicating no tumorous potential of transplanted hMAPCs in
the tumor-sensitive immunodeficient SCID model.

Conclusions:

Transplantation of human MAPCs after MI ameliorates myocardial function, which may be explained by hMAPCs’ potential to integrate into vessels and myocardial structures in the borderzone and form smooth-muscle-cell-like as well as cardiomyocyte-like cells. Lack of evidence of tumorous potential in the tumor-sensitive SCID model indicates, that hMAPC may deliver not only an effective, but also safe stem cell pool for the treatment of MI.