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Biodistribution and effects of IV-Injected mesenchymal bone marrow cells in a mouse model of chagas disease

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hagas disease, resulting from infection with the parasite Trypanosoma cruzi, is a major cause of cardiomyopathy in Latin America. Treatment options are limited to a small number of drugs that were developed more than four decades ago and which have various drawbacks. Stem cell therapy with bone marrow mesenchymal cells (MSCs) has emerged as a novel therapeutic option for cell death-related heart diseases, but efficacy of MSCs has not been tested in Chagas disease therapy. We have used cell tracking strategies following labeling of MSCs with nanoparticles to investigate migration of transplanted MSCs in a murine model of Chagas disease, and have correlated MSCmigration with cardiac function in chagasic animals by magnetic resonance imaging (MRI) and microPET. We also quantified the expression of metalloproteinase (MMP) using a metalloproteinase fluorescence probe (MMPSense750) in chagasic animals treated with MSCs. Mice were intraperitoneally infected with 5 x 10⁴ trypomastigotes and treated by tail vein injection of MSCs, at 1 or 2 months after infection. MSCs were labeled with fluorescent nanoparticles (X-Sight761, Carestream) and were tracked by in vivo imaging system (IVIS). Our IVIS results at two days after transplant showed that a small, but significant, number of cells migrated to chagasic hearts when compared with control animals, whereas the majority of labeled MSCs migrated to liver, lungs and spleen. MRI and microPET techniques showed that therapy with MSCs reduced right ventricular dilatation that is typical of the chagasic mouse model. Additionally, the MMPSense750 showed higher MMP expression in the whole body, heart, spleen and white fat caused by T. cruzi infection. MMP expression in the legs and hind paws was reduced in the chagasic animals treated with MSC. Moreover, we analyzed the expression of several proteins in the heart by Western blot. Proteins as connexin43, laminin y1, IL-10 and INF-y were totally or partially recovered by cell therapy. Other proteins as MMP-2, IL-1β, ZO-1, Occludin, ET-1, STAT1, among others were altered but the cell therapy did not restore them at the studied time points. In summary, the beneficial effects observed by cell therapy in chagasic mice are due to an indirect action of the cells in the heart, most likely through secretion of immunomodulatory and/or growth factors, rather than the generation of new cardiomyocytes or even incorporation of large numbers of stem cells into working myocardium.

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