Detection of Transplanted Stem Cells by Molecular Magnetic Resonance Imaging

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Introduction

Stem cell transplantation is a promising approach for the therapy of various neurodegenerative diseases including Parkinson’s disease (PD). However, the mechanisms of differentiation, migration and long-term survival of the transplanted stem cells are still not clear. In this study, we are magnetically labelling murine embryonic stem cells with iron-oxide particles (VSOP) in vitro to make them detectable by molecular Magnetic Resonance Imaging (MRI).

Magnetic Labelling

We used for cellular labeling Very-Small-Superparamagnetic-Iron-Oxide-Particles (VSOP) C200 (Ferropharm). The VSOP consist of an iron-oxide core, coated by monomer citrate giving a total diameter of 9 nm. The particles are internalized by the stem cells via endocytosis (Fig. 1A, B). As shown in Fig. 2, the incubation with iron-oxide-particles (VSOP) led to a significant uptake of iron by the stem cells measured by Atomic Absorption Spectroscopy (AAS). The intracellular iron concentration is increased by the factor of 49 (1.5 mM VSOP). Therefore, the incorporated VSOP-particles are responsible for 98% (1.5 mM VSOP) of the total iron in the cell after incubation.

Iron-Oxide-Particles Cause Transient Oxidative Stress

Up to now, the effects of this intracellular labeling on the biology of the cells were not thoroughly investigated. Therefore, we investigated whether the magnetic labelling of macrophages with iron-oxide-particles in vitro results in an increase of oxidative stress. We showed that the incubation of macrophages with iron-oxide-particles results in a highly significant increase of oxidative stress. The decrease of oxidative stress to control levels one day after incubation indicates that the augmentation of oxidative stress is transient and closely linked to the incubation of the cells with iron-oxide-particles (Fig. 3). The magnetic labeling is stable over an extended period of time (Fig. 4). The oxidative stress can be reduced by the application of iron-chelators (Desferal).

Detection of Minimum Cell Numbers by High-Resolution Magnetic Resonance Imaging (17 T)

The embryonic stem cells were labelled with 1.5 mM VSOP-particles in vitro. In gel-phantoms 1000 (Fig. 7) and 100 (Fig. 8) magnetically labelled embryonic stem cells can be detected by high-resolution MRI at 17 T. Transplantation of magnetically labelled embryonic stem cells into the striatum of Wistar-rats led to a significant contrast at T2*-weighted images. The hypointensity is dependent on the cell number. Figure 9 shows in vivo MRI at 17 T of 1000 cells. Figure 10 of 100 cells. After transplantation of 1000 unlabelled cells (Fig. 11) only weak T2*-weighted signal changes can be observed, which seemed to be already differentiated (Fig. 12).

Conclusions

This results show that a non-invasive tracking of transplanted embryonic stem cells by molecular MRI is possible. The cells are detectable at very low cell numbers (<100). The next steps are the long term monitoring of the transplanted cells and the establishment of the magnetic labeling as vitality marker also in vivo.

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