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The effect of nanoparticle labeled bone marrow-derived mesenchymal stem cells as a therapeutic strategy for experimentally induced liver fibrosis in albino rats

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Abstract

Objectives: This study aims at exploring the therapeutic efficacy of superparamagnetic iron oxide nanoparticles (SPIO) labeled bone marrow derived mesenchymal stem cells (BM-MSCs) on carbon tetrachloride (CCl4) induced liver fibrosis in adult female albino rats.

Material and methods: MSCs were obtained from 10 male Sprague Dawley rats and 50 female rats were assigned into 2 groups; control group (CG) and experimental group (EG). EG was subdivided into three subgroups. Induction group by intraperitoneal injection of CCl4 for 8 weeks, MSCs treated + CCl4 group (MSCs+CCl4G) received SPIO- BM-MSCs simultaneously with CCl4 administration to assess the effect of SPIO-BM-MSCs on the prevention of progression of liver fibrosis with the persistence of the cause. MSCs treated group (MSCsG), received SPIO-BM-MSCs after withdrawal of CCl4. The rats were sacrificed after 8 weeks and assessed by histological examination, liver function tests, transforming growth factor-beta (TGF-ß1) immunofluorescence staining, PCR for quantification of the gene expression levels of matrix metalloproteinase-1(MMP-1) and tissue inhibitor of metalloproteinase-1 (TIMP-1).

Results: SPIO labeled MSCs were engrafted in the fibrotic liver and MSCs improved liver functions, enhanced the gene expression of MMP-1, whereas TIMP1 gene expression was depressed. Histological and morphometric studies confirmed these results.

Conclusion: BM-MSCs prove to be a promising therapy for liver fibrosis.

Introduction

Stem cells have emerged as a novel therapeutic option for cell death-related diseases, such as myocardial infarction. The effects of adult stem cells on damaged tissues are currently attributed mainly to proliferation, inhibition of apoptosis and inflammation, and increase in angiogenesis caused by the secretion of paracrine factors by injected stem cells, thus stimulating tissue regeneration and repair. However, the difficulty of evaluating and determining the precise contribution of each mechanism involved in cell-based treatments is one of the obstacles to their approval for clinical use. Methods to determine the biodistribution and fate of injected cells are required to understand and refine stem cell therapies in patients. The outcomes of clinical trials using stem cells are less assessable by invasive methods, which are usually used in experiments with animal models and include postmortem analyses, such as histologic analysis of tissues and organs. Currently, there are active efforts to develop and standardize suitable noninvasive methods for long-term tracking of cells after transplantation.9 Magnetic resonance imaging (MRI) offers an imaging modality that allows highresolution visualization of cell biodistribution. Several types of contrast agents have been used for MRI in vivo imaging, including superparamagnetic iron oxide nanoparticles (SPIONs), which successfully label different mammalian cell types. In this review, we discuss the main characteristics and limitations of molecular imaging technologies to investigate cellular biodistribution and fate. The primary focus was on SPION labeling methods for stem cells tracking in a myocardial infarction model, but we also discussed other models, markers, and molecular imaging techniques. We have reviewed the literature in the field and also provided unpublished data on mesenchymal stem cells labeling and tracking in the myocardial infarction model. For this review, we consulted relevant articles published on prominent journals for each specific area covered in the topics, provided that they were indexed on PubMed, Wiley's Library, Science Central, and/or Google Scholar.

Labeling stem cells and molecular imaging methods

Two main approaches are used to label cells for in vivo tracking: direct and indirect labeling. Direct labeling involves a relatively simple step of in vitro incorporation of the marker molecule before the cell therapy. A range of molecules can be used, and this technology is considered fairly well established and yields consistent and reproducible results. SPIONs, fluorescent dyes, or radionuclides can be used as probes to directly prelabel stem cells for noninvasive tracking. Standardized protocols used for labeling stem cells with SPIONs were previously compiled by us,15,24 and other direct-labeling reagents were reviewed by Marks and Nolan25 and Progatzky et al.26 Indirect labeling is a considerably different method, which includes genetic modification in order to either produce an appropriate signal-generating molecule or increase the affinity of cells to contrast agents. Transient expression of reporter proteins by DNA vector transfection is often included in this set of cell labeling. Another alternative is stable expression of the reporter protein by transduction of the cells with a virus. Differently from transient expression, stably transformed cells will continue to produce the protein of interest for long periods and allow us to monitor not only its biodistribution and cell fate but also cell proliferation, considering that the daughter cells will also produce the marker. Indirect and direct methods might serve the purpose of successfully labeling stem cells for noninvasive tracking in vivo. The term "molecular imaging" can be broadly defined as the in vivo characterization and measurement of biological processes at the cellular and molecular levels.33 Here, for our purposes, molecular imaging methodologies are related to the observation of specific cell markers present in the injected cells, in order to follow their biodistribution in a time-dependent manner with noninvasive methods. The different cell markers available can be monitored in vivo by various imaging methods. James and Gambhir, Chen and Zhang et al.36 For preclinical or clinical studies, it is essential to consider the advantages and disadvantages of each molecular imaging modality.

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