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Granulocyte-macrophage progenitor cells response to magnetite nanoparticles in a static magnetic field

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ABSTRACT

The ability to modulate the life process of stem cells conjugated with MNPs via a magnetic field is promising as multifunctional tool in biomedicine. Experiment on mice demonstrates the high accumulation of iron ions measured via stripping voltammetry in the bone marrow in respect to bone, liver or kidney. Therefore, the potential cytotoxic effects of iron oxide magnetic nanoparticles (MNPs) on bone marrow cells become more predictable in comparison with the other examined cells. This study examined *in vitro* responses of mouse bone marrow-derived granulocyte–macrophage committed stem cells (colony-forming units of granulocytes and macrophages, CFU-GM) to a controlled amount of MNPs prepared by the exploding wire method; and to a moderate static magnetic field (SMF) of about 160 Oe. The moderate SMF did not affect CFU-GM capacity. Two different regimes of bone marrow cells cultivation with MNPs were investigated. Remarkably, adding MNPs to cells either decreased (1st cultivation regime, 6 pg MNPs per 1 cell) or enhanced (2nd regime, 20 pg MNPs per 1 cell) the colony-forming activity of CFU-GM, depending on the regimes of cultivation. The action of a moderate SMF on cells cultivated with MNPs inverts their effects on stem cell colony formation. Possible mechanisms of these phenomena are discussed. The main pathway was explained by a change in the presence of iron, either inside or outside of the cell, following the formation of free radicals susceptible to SMFs. Nanoscale magnetite activity within the pool of bipotent hemopoietic stem cells supports its proposed usage as supplement in cell technologies, theranostics, bone marrow repair and regenerative medicine. Further study is necessary to examine the intra- and intercellular mechanisms of the SMF's modulating effect on stem cell activity caused by magnetite MNPs.

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1. Introduction

Nanoscale magnetite (Fe_3O_4) is widely employed both in nature and in themodern human world: in geomagnetic orientation of organisms [1] as well as in multiple medical applications [2] including magnetic resonance imaging (MRI) [3], magnetocontrollable drug delivery systems [4], cellular labeling and targeting, and cell separation and transfection [5,6]. Iron oxide magnetic nanoparticles (MNPs) are promising in bioapplications due to their strong biocompatibility properties and high magnetization value [7]. However, despite active research in recent years, the nature of connection of size, shape, composition, shell-core structure of MNPs synthesized by different chemical and physical methods with their magnetic properties (saturation magnetization, coercivity, blocking temperature, relaxation time) has not been fully investigated. Therefore, understanding and predicting mechanisms of MNP property formation is a complicated task; however, its accomplishment could provide opportunities to fine-tune MNPs with pre-defined properties for their specific biomedical application [8]. Moreover, different mechanisms of MNPs effect on biological systems, such as their toxicity, along with the influence of

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MNPs in the presence of magnetic fields (MFs), are topics of considerable interest [9].

All potential and existing applications of MNPs require their injection into the blood and tissue. Beyond that, nanoparticles may enter the body due to the wear of implants and endoprosthesis and are between 40 and 50 nm in size [10]. The circulatory system, central nervous system (CNS), respiratory and gastrointestinal tracts are the targets for exogenous and endogenous (from implants) nanoparticles. MNPs with a diameter of <50 nm circulate in the blood stream for much longer than larger particles; they, can cross capillary walls, penetrate tissue barriers, and are often extensively absorbed by bone marrow [2]. Consequently, understanding the potential toxic effects of MNPson bone marrow cells is critical from an application perspective. The *in vitro* toxic effect of Fe_3O_4 MNPs on hematopoietic islands (HIs) in mouse bone marrow has been previously demonstrated [11]. HIs are structural and functional units (niches) of bone marrow [12] in which hematopoietic stem cells including granulocyte/macrophage progenitor cells proliferate and differentiate into mature blood elements [13]. Because granulocytes and monocytes are phagocytes, they should be cellular targets for MNP activity and cytotoxicity. At the same time, no morphofunctional changes of phagocytising mesenchymal stem cells were revealed in conditions of their *in vitro* contact with iron oxide MNPs in the Fe concentration range from 2 to 1000 of maximum tolerated doses [14]. Hence, it seems reasonable to evaluate the risk and benefit ratio for the prospective use of magnetite MNPs in biomedical developments in the field of correction and diagnostics of blood system disorders.

Increasing investigation of the influence of static magnetic fields (SMFs) on life processes derives from concerns about their possible harmful effects on human health. Data reported in the literature are quite heterogeneous [15]. The effects of moderate-intensity (1 mT to 1 T) SMFs on blood cells have primarily been examined *in vivo,* and often with inconsistent results [16]. For example, leukopenia in mice exposed to a 400-mT field was described in one early report [17]; conversely, in another study [18], no alterations were observed relative to white blood cell count. At present, there is a shortage of conclusive evidence in this area due to the vast variation of field strength and exposure duration used in different studies. Moreover, biological impacts of SMFs depend on cell type, age, and stage (e.g. mitosis or differentiation). It is therefore challenging to compare results obtained from different investigations.

As new technologies are introduced, such as magnetically levitated trains and therapeutic use of MFs increases (e.g. MRI, coupling of MF exposure with chemotherapy and MNPs), a more comprehensive of the biological effects of SMFs on living organisms and cells becomes essential in order to protect human health. However, neither acute exposure nor exposure in the working environment to SMFs at flux densities below 2 T has been unequivocally found to have adverse health consequences [15].

Presently, knowledge of the effects of SMFs on cell proliferation and differentiation is scarce and controversial [15]; furthermore, only a limited number of studies have examined the combined action of magnetite MNPs and moderate SMFs on the hematopoietic stem cell pool and committed stem cells of granulocytes and monocytes, in particular [19]. However, the colony-forming units of granulocytes and macrophages (CFU-GM) assay detects the direct adverse effects of irritants on the proliferative capacity of bi- and unipotent hemopoietic stem cells, and should be able to predict the exposure dose that would cause neutropenia [20] accompanied by severe infectious complications.

In this work we examined target mouse tissue for iron ion accumulation. *In vitro* morphofunctional response of mouse bone marrow-derived granulocyte-macrophage stem cells to magnetite MNPs, moderate-intensity SMF and their combined effect was studied. Two regimes of mouse bone marrow cells (BMCs) cultivated with iron oxide MNPs were tested due to the practical diagnostic and therapeutic need to introduce nanoparticles into the cells *in vitro,* and into the blood and tissue *in vivo*.

2. Materials and methods

2.1. Preparation of nanoparticles

Iron oxide MNPs were obtained via the exploding wire method. A detailed description of the methodology and the experimental setup used in the present study are available elsewhere [21]. The X-ray diffraction (XRD) studies were performed with a Shimadzu XRD-6000 diffractometer (Tokyo, Japan). For qualitative analysis of the phase composition, the PDF4 + computer database of X-ray powder diffractometry of the International Center for Diffraction Data (ICDD, Denver, USA) was used. POWDER CELL 2.4 software with full profile analysis was employed for the quantitative analysis. Transmission electron microscopy (TEM, Tecnai 20 G2 TWIN, FEI Company, USA) was used for MNP morphology and size distribution investigations; the selected-area electron diffraction (SAED) pattern was measured inside the TEM to identify the phase composition.

Measurements of MNP magnetic properties were performed with a VSM magnetometer (7400 System Vibrating Sample Magnetometer, Lake Shore Cryotronics Inc., USA) in a field range of up to 11 kOe at room temperature (295 K). Field dependents of magnetization and remanent magnetizations were obtained in two ways: i) after demagnetized state (M_{IRM}) and ii) after saturation in opposite direction (M_{DCD}). Analysis was performed using the Henkel Plot method following the algorithm described in [22].

Before preparing the suspension for biological testing, the iron oxide MNPs were dry-heat sterilized with Binder FD53 (Binder GmbH, Tuttlingen, Germany) at 180 °C for 1 h.

To study chemical and biological features, we used a 3 mg/L iron oxide MNP suspension in isotonic (0.9%) sterile *NaCl* solution, equivalent to 10 maximum tolerated doses (MTD) for Fe ions in water solution. This concentration of iron oxide MNPs was not toxic for human mesenchymal stem cells [14] and murine hemopoietic cells [19] in our previous experiments. De-aggregation of agglomerates in MNPs suspension was ensured by ultrasound treatment on Elmasonic S 30/H (Elma Hans Schmidbauer GmbH & Co, Singen, Germany) operated at a power output of 320 W for 10 min.

2.2. Electrochemical testing

The distribution of iron ions in mouse biological tissue (bone marrow, bone, liver, and kidney) was studied by stripping voltammetry (SV) [23] in an analytical laboratory in Tomsk Polytechnic University (Tomsk, Russia) certified for measurement of trace elements (government accreditation certificate RA.RU.21AB16 from 10.04.2015). Nine CBA/CaLac mice were used with approval from the Local Ethics Committee of Siberian State Medical University (Tomsk, permission No. 1923 from 28.03.2011). The animals were sacrificed by ether overdose. Bone marrow from the femur, the femur itself, a single kidney, and sample weights of liver (0.5–1 g) were isolated. Mass concentration units (mg/kg) of Fe ions were determined in tissues and organs.

2.3. Cell culturing in vitro

A primary culture of mouse BMCs was used. BMCs (myelocaryocytes) were collected from femurs and co-cultured with iron

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