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Humoral immune response against allogeneic equine mesenchymal stem cells (MSCs) mediated by the major histocompatibility complex (MHC): an issue to take into account for the safety and efficacy of treatment with MSCs

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Allogeneic mesenchymal stem cells (MSCs) present several advantages, but recipient immune response needs to be further elucidated. Proinflammatory priming of MSCs activated their in vivo regulatory capacity, but repeated administrations led to slight inflammatory reaction in an osteoarthritis equine model. This may be associated with higher major histocompatibility complex (MHC) expression, which would increase MSC immunogenicity potentially inducing humoral mediated immune memory. This study aimed at assessing allo-antibody production against donor's equine MHC (equine leukocyte antigen, ELA) in animals that received intra-articular repeated administration of allogeneic MSC-primed. For this purpose, we used stored samples from a previous study. Donor and recipients ELA-haplotypes were stablished by microsatellite typing and complement-mediated microcytoxicity assays were carried out by exposing target cells from the donor (unstimulated MSCs [MSC-naïve], MSC-primed or lymphocytes [control]) to sera collected at different time-points from 10 recipients: ELA-mismatched MSC-naïve recipients, ELA-mismatched MSC-primed recipients or ELA-partially matched MSC-primed recipients. All animals receiving allogeneic MSCs produced allo-antibodies after the first injection, regardless of the matching degree. However, antibody peak production after second administration was only observed in ELA-mismatched recipients, both of MSC-naïve and MSC-primed. Horses injected with MSC-primed produced fewer antibodies but MSC-primed were more targeted in the microcytoxicity assay. Thus, activated immunomodulatory profile of MSC-primed could have led to slighter humoral response after first administration, but these cells would be more easily targeted by existing antibodies post-second injection. Allo-antibody production against allogeneic equine MSCs could explain their time-limited efficacy and may affect the safety and efficacy of this cell therapy.

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IL-4 gene overexpression promotes repair of the ischemic skeletal muscle

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Peripheral arterial disease is caused by atherosclerosis that leads to obstruction of arteries and inflammation. Macrophages and monocytes sub-types participate in different stages of repair and regeneration of the ischemic limb, controlling angiogenesis, myogenesis, fibrogenesis and proliferation of local cells. Here we aimed to evaluate effects of exogenous IL-4 gene expression over monocytes/macrophages and in the ischemic skeletal muscle. Limb ischemia was induced by electrocauterization in the left femoral artery of male Balb/c mice at 10–12 weeks old age. Three days later, this limb was electroporated with 50 μg of IL4-expressing plasmid vector (uP-IL4). In the blood, Ly6C+ monocytes decreased 34.6 ± 3.6 % (before ischemia) to $15.2 \pm 7.2\%$ and $24.8 \pm 0.8\%$ 4 days after electroporation with uP-IL4 and uP (empty vector), respectively. The tissue macrophages (F4/80+/CD206+/MHCII-) were $8.2 \pm 1.4\%$ prior to ischemia that changed to $8.3 \pm 4.0\%$ and $22.5 \pm 4.3\%$ 2 days after electroporation with uP and uP-IL4, respectively. Visual analysis of the mouse pads showed improvement with uP-IL4 treatment in comparison to the untreated group, but no significant superficial blood flux was found between them. However, the ratio of muscle force and muscle mass after 4 weeks showed a complete recovery with uP-IL4 treatment, while the control groups recovered only 50%. In histology, we found that uP-IL4 treatment reduced adipocytes and myofibers with peripheral nuclei, showing healthier and normalized skeletal muscle. Collectively, it seems that the overexpression of IL-4 in the ischemic limb recruited more anti-inflammatory monocytes and macrophages temporarily, which promoted ischemic muscle repair and regeneration with less adipocytes.

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Differentiation potential of stem cells cultured on glass surfaces coated with magnetic nanoparticles

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Cell-matrix interaction plays a major role in cell differentiation alongside growth factors and cell-cell interactions. Investigation an effective nanomaterials promoting adhesion, proliferation, and differentiation of cells is crucial in tissue engineering. Iron oxide magnetic nanoparticles (MNPs) is one of the promising nanomaterials that may be used to modify cell substrate. The manipulation of MNPs by an external magnetic field allows constructing complex surface for cell culturing. In this study, we investigate the influence of MNPs-based surface on the differentiation potential of adipose-derived mesenchymal stem cells. The study was performed according to Program of Competitive Growth of KFU and funded by the subsidy allocated to KFU (project 16.2822.2017/4.6), the Russian Presidential grant MK-4498.2018.4 and RFBR project № 18-53-80067. MNPs were synthesized by the method of chemical reduction and characterized by both atomic force (AFM) and hyperspectral dark-field microscopy (HSM). Next, the surface of MNPs at concentrations 0.3–1.2 mg/ml was constructed by the method of colloid immobilization. The roughness of samples was analyzed by AFM. Biocompatibility of samples was measured by MTT-assay. Differentiation of cells into chondrocytes,