Mesenchymal stem cells as potential immunosuppression in skeletal muscle cell therapy - studies in a mouse model

Skeletal muscles are characterized by the enormous ability to regenerate after the injuries. Regeneration depends on muscle specific stem cells - satellite cells. Satellite cells become activated only after the tissue is damaged: this is when they start to act: they proliferate, differentiate into myoblasts, fuse and finally replace the damaged myofibers. Some of them return to the quiescent state to restore their population. However, during the progression of certain diseases, such as Duchenne's muscular dystrophy (DMD), the ability of skeletal muscle to regenerate is impaired. In such disorders the improper muscle structure leads to the repeating injuries and under such conditions satellite cells cannot “keep up”, replace all of the missing myofibers and their own population. For these reasons satellite cells are quickly depleted. As a result, skeletal muscle tissue is replaced by the connective tissue. Currently, there is no effective treatment for DMD or other muscle-wasting diseases, such spinal muscle atrophy. One of the proposed therapies is based on the transplantation of functional satellite cells into the muscle. Unfortunately, successful cell therapy for dystrophies or massive muscle injuries has not been designed yet, due to the number of reasons. First, the satellite cell isolation requires extensive biopsy of skeletal muscle of the potential donor. Secondly, no efficient method for satellite cell propagation in the laboratory was described – and propagation of isolated cells is crucial to obtain sufficient numbers of cells for transplantations. Next, satellite cells (isolated from the health donor) could be eliminated by the host’s immune system. There is, however, an alternative source of satellite cells for treatment: pluripotent stem cells. Pluripotent stem cells, such as embryonic stem cells, are able to differentiate into all cell types building the mammalian body, skeletal muscle myoblasts and satellite cells included. For many years, no protocol for efficient pluripotent stem cells differentiation into myoblasts was available. In 2015 the efficient method for pluripotent stem cells differentiation into myoblasts and satellite cells was described. Importantly, the cells obtained with proposed protocol were able to participate in skeletal muscle regeneration in mice. However, the experiment proving functionality of these cells was performed on immunodeficient mice were used. Therefore, the experimental setting did not reflect the challenges that need to be overcome before stem cells are applied in medicine. In immunocompetent host cells obtained from differentiated pluripotent stem cells will be treated as “foreign” by the immune system and eliminated. The immunosuppressive drugs can block the activation of immune system preventing the elimination of transplanted cells. However, these medications can have potentially dangerous adverse effects. In skeletal muscles immunosuppressive drugs (i.a. tacrolimus) can perturb myoblasts fusion which is the crucial step for tissue reconstruction. For this reason, other approaches to modulate immune response, such as mesenchymal stem cells (MSCs), are tested. MSCs have immunomodulatory properties: they interact with immune cells in various ways and can influence their functions. Because of this, MSCs are tested as a treatment for the diseases caused by the chronic inflammation, such as arthritis. It was also reported that MSCs can prolong graft’s survival after the skin transplantations and alleviate the Host *versus* Graft Disease, which can develop after the transplantation of bone marrow. Based on these previous observations I decided to test whether it is possible that MSCs could replace the traditional, i.e. drug mediated, immunosuppression following the cell transplantation also in skeletal muscles. In the proposed project I will address the question whether MSCs (or factors secreted by them) transplanted with satellite cells derived from pluripotent stem cells would be able to prevent the rejection of the engrafted cells. Thus, I aim to provide evidence that MSCs could replace the immunosuppression in skeletal muscle cell therapies. This issue has not been studied, yet, and for this reason obtained results can contribute to the development of regenerative medicine.