

*The role of microRNA-378 in fibro-adipogenic progenitors (FAPs) during muscle regeneration*

Skeletal muscles are the most abundant and dynamic tissue in the human body. They represent 40% of the body mass and contains 50-70 % of all body protein. Unfortunately, they are also constantly exposed to injuries and need to be regenerated. Muscle regeneration is a very complex and strictly regulated process with many cell types including inflammatory cells, muscle satellite cells (mSC) and fibro-adipogenic progenitors (FAPs), collaborating with each other. Muscles are like little factories with cells being delegated to perform certain tasks, which has to be executed at a specific time. If there is some delay or some part of such a system is not working properly, the whole machinery may fall apart. Such a situation can be observed in various pathological conditions, including incurable so far Duchenne muscular dystrophy (DMD).

DMD is caused by mutations in the dystrophin coding gene. Dystrophin is a large structural protein that is essential for the proper connection between the actin cytoskeleton filaments and extracellular matrix proteins. Absence of dystrophin makes the muscles extremely sensitive and prone to mechanical damage and as a result causes the continuous activation of skeletal muscle satellite cells (i.e. stem cells, which normally are activated, for example in the injured muscles or after training), induction of inflammation, fibrosis and fatty tissue accumulation. All these processes lead to a progressive loss of muscle mass and muscle dysfunction. In order to find new treatments scientists follow various strategies, including modifications of the muscle fibers environment. The focus of our proposal concentrates on the cells responsible for the fibrosis and adipose tissue accumulation in pathological conditions, meaning FAPs.

FAPs are mesenchymal progenitor cells with the capacity to differentiate in both fibroblasts and adipocytes. In the successful regeneration, they support mSC in the process of myogenesis but in DMD, due to dysregulation of regulatory signals, their fate takes a more sinister turn, causing extensive accumulation of connective tissue and adipocytes. In order to better understand their differentiation commitment, it is important to find new modulators of such process. In the frame of the presented proposal, we decided to investigate the role of miR-378, a small non-coding RNA molecule that is able to regulate the expression of various genes. Despite the known and studied also by our group role of this miRNA in muscle and lipid-related processes, the connection between miR-378 and FAPs was not considered so far.

In the current project, we will test the hypothesis that the lack of miR-378 affects FAPs differentiation commitment during muscle regeneration and their interaction with mSC. Moreover, we believe that it may lead to the acceleration of the regeneration process, reduced fibrosis, and fatty tissue accumulation and as a result, increased maximal muscle force during a functional test.

To examine our hypothesis, we will conduct experiments using a mouse model of muscle injury. Mice globally lacking miR-378 and their wild type counterparts will be injected intramuscularly with the glycerol and at various time point within the 28 days long regenerating process we will assess muscle damage, following inflammation, fibrosis, adipose tissue and markers of regeneration like for example number of the fibers with centrally oriented nuclei. In order to check FAPs functionality, cells will be an isolated and global analysis of gene expression will be performed. At the end of the experiment, on day 28 muscle contraction will be assessed, giving us information about potential functionality changes.

The results of the project will broaden our knowledge about the role of miR-378 in FAPs and their differentiation commitment. We do believe that carefully planned analysis will shed more light at the neglected so far topic and maybe provide a novel therapeutic approach for DMD patients.