Project 1.9 How mutations in the dystrophin-encoding gene affect calcium homeostasis, energy metabolism and selected functions of vascular endothelial cells; indicating regulatory mechanisms

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Background:

Duchenne muscular dystrophy (DMD) is the most common inherited human muscle disorder caused by mutations in the dystrophin encoding gene and complete lack of this protein. Dystrophin gene has 7 promoters; 3 of them are responsible for full dystrophin (Dp 427 kDa) biosynthesis, while remaining four promoters localized within this gene control an expression of shorter protein variants. Experimental data indicate that an aberrant cellular Ca2+ homeostasis accompanying DMD is at least partially responsible for pathological consequences of dystrophin deficiency. It was confirmed not only in muscle fibres but also in myoblasts (from mdx mice, an animal model of DMD), lymphoblasts from DMD patients, dystrophic circulating CD133(+) stem cells and other. Thus, though life-threating symptoms of dystrophin deficiency come from a severe muscular dysfunction, DMD affects many other organs including endothelium.

Literature data clearly show that dystrophin deficiency impairs endothelial cells and results in improper angiogenesis, motility and tube formation. However, biochemical mechanism behind these effects are still obscure.

Although endothelial processes are tightly regulated by Ca2+, effects of DMD on Ca2+ signalling in endothelial cells have never been investigated. Similarly mitochondrial metabolism which is mutually related to Ca2+ homeostasis has not been explored in DMD endotheliocytes. Understanding a role of dystrophin in maintaining of the proper Ca2+ signalling in endothelial cells is an interesting challenge not only for its cognitive value but also it may deliver a knowledge potentially useful for relieve some DMD symptoms. All experiments will be performed with the use of primary endothelial cells isolated from healthy and dystrophic mice.

Aim:

Identification of endothelial consequences of DMD. This project is focused on the basic research but potential application of results might also be considered in the future.

Requirements:

- the perfect candidate graduated from a faculty of biology or similar (veterinary, pharmacy), with special focus on biochemistry or animal physiology,
- an experience in experiments on animals (preferably mice) will be appreciated, moreover the candidate must be ready to conduct long-lasting experiments, which require patience, accuracy and perseverance,
- a thorough knowledge of written and oral English is required.