„Role of liprin-α-1 in development and maintenance of the Neuromuscular Junction postsynaptic machinery”

Breathing and coordinated movements are principal features of our organism without which we cannot survive. These processes are controlled by the Central Nervous System (CNS), which receives signals from the environment. In order to reach the muscle surface, nervous impulses originate in the brain and are transmitted along the spinal cord to the motor neurons. Motor neurons make long axonal projections that innervate each fiber in our skeletal muscles. The connection between the neuron and muscle is called neuromuscular junction (NMJ). The NMJ is a chemical synapse, which mediates signal transmission from the nerve to the muscle by chemical neurotransmitter acetylcholine (ACh). ACh is released from the nerve terminal, crosses a physical space called the synaptic cleft and binds to acetylcholine receptors (AChRs) clustered on the muscle surface. Upon binding, activated AChRs trigger cascade of signals on the muscle surface that generate muscle action potential along the sarcolemma and in the end leads to muscle contraction.

The major components of the NMJ postsynaptic machinery are AChRs, which in a very high density are clustered and stabilized on the muscle surface. The density of AChRs at NMJs is critical for muscle function because it determines the effectiveness of neuromuscular transmission. The molecular machinery that is responsible for receptor stabilization and turnover and therefore maintenance of proper receptor density, is poorly understood. In our laboratory we are identifying new proteins orchestrating development of NMJs. In my research I will study the role of liprin-α-1 in this process. Our preliminary results verified presence of liprin-α-1 at the NMJ postsynaptic site in regions rich of AChRs. Our biochemical experiments suggest a molecular link between liprin-α-1 and the Dystrophin-associated Glycoprotein Complex (DGC), which is known for stabilization of synaptic machinery. It is important to mention that mutations in several DGC components cause sever neuromuscular disorders like Duchenne muscular dystrophy (DMD). From the literature it is also known that liprin-α-1 binds to ELKS, LL5β and CLASP that form a protein complex involved in trafficking of membrane molecules including AChRs. Based on these information we hypothesize that liprin-α-1 can play a crucial role in regulation of postsynaptic AChR, but the function of this protein at the vertebrate NMJ has never been investigated. In my studies I will use variety of sophisticated techniques including RNAi mediated gene silencing, immunocyto- and immunohistochemistry, electroporation of plasmid DNA in muscle and confocal microscopy.

Our research could provide not only basic knowledge about synaptic development, but also could help in designing strategies in therapy of serious neuromuscular disorders like DMD. This disease affects on average 1:3500 boys. At the beginning of the disease at the age of 3-8, patients start to lose their muscle strength and as the disease progresses it affects walking and breathing. No treatment for this disease is currently available. The Duchenne muscular dystrophy is caused by a mutation on the X chromosome in the gene coding dystrophin, which is a component of the NMJ postsynaptic machinery. Our research on other DGC component, liprin-α-1, will be likely an important contribution in the field of neurobiology. Obtained results have a potential to be published in recognized international scientific journals.