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“The role of the actin-remodeling proteins Cap2 and Cttn in the development of the neuromuscular synapse”

Ph.D. thesis

Abstract

The neuromuscular junction (NMJ) is a peripheral synapse that connects motor neurons with a highly specialized zone of skeletal muscle fibers and governs essential life functions such as movements and breathing. Structurally, the NMJ is a tripartite functional unit where motoneurons, post-synaptic specialization, and terminal Schwann cells participate to the neuromuscular signaling. The development of NMJ is a multi-stage process that is crucial for the healthy functioning of the synapses.

The cyclase-associated protein 2 (CAP2) and Cortactin (Cttn) are actin-binding proteins (ABPs) that participate to the dynamics of actin-cytoskeleton remodeling by sustaining separate mechanisms. CAP2 is known to be involved in “actin-treadmilling” by promoting the disassembly of filamentous actin (F-actin) at its pointed-end. Furthermore, CAP2 participates in parallel to the mechanism of globular actin (G-actin) recharging, an essential step for the re-incorporation of actin monomers within the filaments. Whereas, Cttn, participates to the action of Arp2/3 complex, thus it is implicated in remodeling mechanism that polymerases branches of actin from a pre-existing filament and increases the complexity of actin-meshwork.

Actin cytoskeleton underpins multiple stages of synaptic formation, participating to both pre-synaptic and post-synaptic events. Furthermore, actin-cytoskeleton is important for maintenance of synaptic integrity through lifespan. The disruption of actin dynamics impairs the healthy functioning of these synapses. In vertebrates, CAP2 is expressed in muscles and the heart and the brain, suggesting a specific role in these organs. My study provide in-depth characterization of CAP2 phenotype at the peripheral synapses and I reported that CAP2 is a novel key organizer of NMJ.

The dystrophin-glycoprotein complex (DGC) is a transmembrane multi-protein complex that stabilizes the post-synaptic apparatus of NMJ by linking the extracellular matrix (ECM) to the intracellular cytoskeleton. Our long-term studies focus on the understanding the molecular functions of one core DGC cytoplasmic components, named α-Dystrobrevin 1 (αDB1), which plays a role in synaptic stabilization. αDB1 functions as a recruiter for peripheral partners of the DGC at the NMJ and Cttn emerged as interactor of αDB1 from our preliminary screening based on mass spectrometry. In my study revolving around the role of Cttn at NMJ, I confirmed that Cttn is interactor of αDB1 at NMJ and provided deep characterization *in vivo*.