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The roles of dystrophin and dystrobrevin : in synaptic signaling in drosophila

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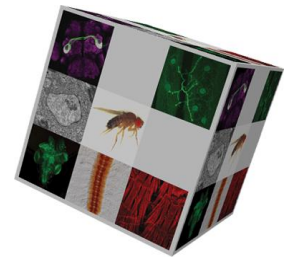
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Propositions

Belonging to the dissertation



The Roles of Dystrophin and Dystrobrevin in Synaptic Signaling in *Drosophila*

1. The Rho-GAP Crossveinless-c, a negative regulator of Rho-GTPase signaling pathways, genetically interacts with Dystrophin and Dystrobrevin (this thesis)
2. Loss of Dystrophin results in the delocalization of Dystrobrevin from the postsynaptic region of the NMJ. This, in turn, causes a reduction in the activity of the Rho-GAP Crossveinless-c leading to an increased activity of the Rho-GTPase CDC42 (this thesis)
3. The Ca^{2+} /calmodulin-dependent kinase II (CaMKII) is a postsynaptic target of Dystrophin, acting downstream of CDC42 (this thesis)
4. Dystrobrevin acts via the regulatory subunit of protein kinase-A (PKA-R). Expression of constitutively-active PKA, either pre- or postsynaptically, rescues the *Dystrobrevin* mutant increased neurotransmitter release phenotype (this thesis)
5. The CNS-specific Dystrophin isoform, Dp186, is required to maintain wild type synaptic transmission in the olfactory system (this thesis)
6. CaMKII activity controls retrograde signaling and presynaptic BMP receptor *wishful thinking* (*wit*) is required for this retrograde signaling to function (Haghighi et al. Neuron. 2003;39(2):255). *wit* also is required for the increased neurotransmitter release in the Dystrophin DLP2 null mutant (van der Plas et al. J. Neurosci. 2006;26(1):333). These results suggest that CaMKII and Dystrophin may use the same retrograde signaling pathway controlling the synaptic homeostasis.
7. The Schizophrenia susceptibility gene, *dysbindin* or Dystrobrevin-binding protein 1, is required presynaptically for the homeostatic modulation of neurotransmission at the *Drosophila* NMJ (Dickman & Davis, Science. 2009;326(5956):1127). It is conceivable that this protein interacts with Dystrobrevin at this site.
8. Ephexin, the Rho-type guanine nucleotide exchange factor (Rho-GEF), and Cdc42 couple synaptic Eph signaling to the modulation of presynaptic $\text{Ca}_v2.1$ channels during the homeostatic enhancement of presynaptic release at the *Drosophila* NMJ (Frank et al. Neuron. 2009;61(4):556). It is possible that a presynaptic role of Dystrobrevin is required in this pathway.
9. The murine Dystrophin isoform Dp71 plays a role in glutamatergic synapse organization and function in the brain. Dp71-null mice show stronger learning impairments than *mdx* mice supporting the hypothesis that Dp71-deficiency contributes to the cognitive deficits in Duchenne muscular dystrophy patients (Daoud et al. PLoS One. 2008;4(8):e6574).
10. "After climbing a great hill, one only finds that there are many more hills to climb." (Nelson Mandela)
11. "When another person makes you suffer, it is because he suffers deeply within himself, and his suffering is spilling over. He does not need punishment; he needs help. That's the message he is sending." (Thich Nhat Hanh)
12. "One of the things I learned when I was negotiating was that until I changed myself, I could not change others." (Nelson Mandela)
13. "There are only two mistakes one can make along the road to success; not going all the way, and not starting" (Buddha)