Non-apoptotic role of caspase-3 in synapse refinement

With the support by the National Natural Science Foundation of China, Dr. Luo Zhen'ge's laboratory at the Institute of Neuroscience, Chinese Academy of Sciences published a research article entitled "Caspase-3 cleavage of dishevelled induces elimination of postsynaptic structures" in *Dev Cell* (2014, 28(6): 670—684).

Caspase-3, the effector protease among mammalian caspases, plays a critical role in apoptosis. Interestingly, growing lines of evidence have shown the physiological functions of caspase-3 in mediating non-apoptotic processes, including neural development and plasticity. The clustering of neurotransmitter receptors is a hallmark for postsynaptic differentiation. This study has provided strong evidence supporting another non-apoptotic role of caspase-3 in neural development. At the vertebrate neuromuscular junction (NMJ), the clustering of AChRs is believed to be regulated by positive and negative factors, which determine strengthening of innervated AChR clusters and dispersion of aneural clusters, respectively. The interplay between positive and negative signals results in the precise matching of motor nerve terminals to individual postsynaptic sites enriched with AChRs. However, the intracellular interplay between positive and negative signaling remains elusive. In this study, Dr. Luo's team reported that caspase-3 mediates elimination of AChR clusters. They found that caspase-3 was activated by cholinergic stimulation of cultured muscle cells without inducing cell apoptosis and this activation was prevented by agrin. Interestingly, inhibition of caspase-3 attenuated ACh agonist-induced dispersion of AChR clusters. Furthermore, they identified Dishevelled1 (Dvl1), a Wnt signaling protein involved in AChR clustering, as the substrate of caspase-3. Blocking Dvl1 cleavage prevented induced dispersion of AChR clusters. Finally, inhibition or genetic ablation of caspase-3 or expression of caspase-3-resistant form of Dvl1 caused stabilization of aneural AChR clusters. Thus, caspase-3 plays an important role in the elimination of postsynaptic structures during the development of NMJs.

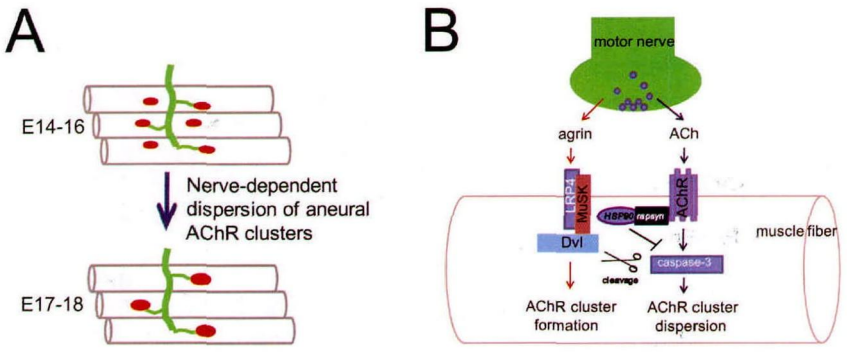

Figure A, Schematic illustration of two overlapping steps in NMJ development. Green, presynaptic nerves; red, postsynaptic AChR clusters. B, Working model. ACh-activation of caspase-3 leads to the cleavage of MuSK signaling protein Dvl1, resulting in the elimination of aneural AChR clusters. Agrin inhibits ACh-induced activation through HSP90β, leading to the stabilization of innervated clusters.