Synapse Formation:
What happens once an axon finds its target?

Changes occur in both pre-synaptic and post-synaptic cells

Specialization for cell-cell communication - SYNAPSE

Pre-synaptic specializations
Vesicle clustering
NT synthesis and release
Cytoskeleton changes
Formation of active zones
Concentration of mitochondria to synapse

Post-synaptic specializations
Clustering of NT receptors (scaffolding proteins)
Morphological changes
  postsynaptic density – CNS
  Membrane involutions - NMJ
Neuromuscular junction (NMJ) is the best studied system for synapse formation.
Synapse formation proceeds in discrete steps

Steps 1 and 2
A growth cone finds and approaches a newly formed myotube and forms a morphologically unspecialized but functional contact.

Step 3
The terminal accumulates synaptic vesicles and a basal lamina forms in the synaptic cleft. Receptors start to accumulate around the nerve terminal.

Step 4
As the muscle matures, multiple axons converge on a single site. Schwann cell starts to wrap around the NMJ.

Step 5
All axons but one are eliminated and the survivor matures.
The clustering of AchRs at the NMJ

During development, AchRs are distributed diffusely on the muscle surface. Nerve innervation triggers redistribution of AchRs.

1) Translocation of surface AchRs.

2) Transcriptional activation of AchRs in the nuclei at the synaptic region.

3) Repression of AchR expression at non-synaptic sites.
The clustering of AchRs at the NMJ

Denervation of the muscle fiber and elimination of mature muscle fibers

Basal lamina sheath is intact

Muscle satellite cells proliferate and differentiate into new muscle fibers

“Synaptic” clustering of AchR in the absence of MN innervation

What is left behind by the MN that clusters AchR?
Agrin released by nerve terminal acts through MuSK and rapsyn to aggregate AchRs at the NMJ

Agrin is a large extracellular matrix proteoglycan that is released by MN.

In the absence of agrin, few AchR clusters are formed.
Agrin released by nerve terminal acts through MuSK and rapsyn to aggregate AchRs at the NMJ

**MuSK**: Muscle-specific tyrosin kinase, Agrin receptor.
Neuregulin stimulates synthesis of AchRs at synaptic sites via erbB kinases
Nerve activity suppresses expression of AchR at non-synaptic sites
Role of muscle fiber in organizing MN terminals
Role of muscle fiber in organizing MN terminals

A. Wild type

B. Laminin β2 mutant

Schwann cell invasion of synaptic cleft in laminin β2 mutant
Synapse elimination as a step of the NMJ maturation
Synapse in the mammalian central nervous system (CNS)

Organization of the CNS synapses follows similar principles used at the NMJ, but less well understood due to its complexity.
**CNS**: receptors at inhibitory and excitatory synapses are organized by different cytoplasmic scaffolding proteins.
Synaptic adhesion molecules link pre- and post-synaptic membranes in the CNS