Neuron-Target Interactions
Pre- and postsynaptic connection
Synapse formation (synaptogenesis)

Synapse formation at the neuromuscular junction
Most well studied system
Synapse formation in NMJ

developing and regenerating synapses co-culture of motor neurons with muscle cells transgenic mice

Growth cones of motor neurons
+ [contact]

Differentiating muscle fibers.

\[ \text{minutes} \]

Functional synapse

\[ \text{weeks} \]

Matured synapse

arborization
withdrawal and elimination of other synapses
Efficient ACh release
modification of postsynaptic membrane

In an adult myofiber (polynuclei) innervated by a single motor axon that arborizes 0.1% of the muscle surface.
Development of neuromuscular junction

E13  Entering of motor axons into developing muscle
     Formation of myotubes by myoblast fusion

E14  Functional synapse detectable

E15-20  Clustering of AChRs near the nerve terminal
        AChE in the synaptic cleft
        synaptic vesicles at the active zone

P0-14  Postjunctonal fold
        synapse elimination
        one motor axon for each muscle fiber

FIGURE 2. Schematic drawing of the major stages of neuromuscular junction
Role of synaptic basal lamina for pre- and postsynaptic differentiation

Damage to the motor axon
Damage to the axon, muscle fiber
Damage to the axon, muscle fiber and Schwann cell

precise re-innervation to the original synapse site
Agrin

Secreted by the nerve
Cause AChR clustering
Localized at the synaptic basal lamina

**FIGURE 19.3** Agrin induces the redistribution of AChRs. (Left) Motor neurons synthesize and secrete agrin into the synaptic basal lamina. Before innervation, AChRs (green) are spread diffusely over the surface of the myotube. (Right) The release of agrin by the motor neuron results in the redistribution of previously unclustered AChRs to synaptic sites, immediately adjacent to the nerve terminal. Through the clustering of existing AChRs and the increased synthesis of new AChRs, the concentration of receptors at the synapse greatly exceeds that in extrasynaptic regions.
MuSK is required for agrin-induced AChR clustering and synapse formation.

1. Agrin or MuSK knockout mice-same phenotype lack of normal neuromuscular synapses
2. Agrin induces rapid MuSK tyrosine phosphorylation.
3. Extracellular domain fragment of MuSK inhibits agrin-induced AChR clustering.

MuSK (muscle-specific kinase)
Receptor tyrosine kinase
Only expressed in muscle but not in neuron
Exact signaling mechanism unknown

Rapsyn (43kDa protein) is likely to be downstream of agrin-MuSK.
Rapsyn knockout mice:
  lack of normal clustering of AChR components in synaptic basal lamina
MuSK
Expression
1. expressed at low levels in proliferating myoblasts
2. induced upon differentiation and fusion (formation of myofiber).
3. dramatically down-regulated in mature muscle,
   remain prominent only at the neuromuscular junction
4. dramatic induction after nerve injury, block of nerve activity,
   and physical immobilization

Interaction
with extracellular domain
   Agrin- in or near the 1st Immunoglobulin (Ig) extracellular domain
   Rapsyn- in or near the 4th Ig domain
With cytoplasmic domain
   PTB (phosphotyrosine binding) domain containing proteins
   PZD (PSD-95/Dlg/ZO-1) domain containing proteins
Synapse-specific gene expression in synaptic nuclei

*It has been postulated that a signal for synapse-specific transcription is contained in the synaptic basal lamina.*

Possible candidate: 
**Neuregulin (NRG) = ARIA (ACh Receptor Inducing Activity)**
- AChR synthesis
- Proliferation of Schwann cells
- Various splice variants in NRG