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Stephan Kröger
Institute for Neurophysiology
Ludwig- Maximilians-University Medical School
Munich, Germany

The Sense of Proprioception and the Development of Muscle Spindles
Part II: Muscle Spindle Development

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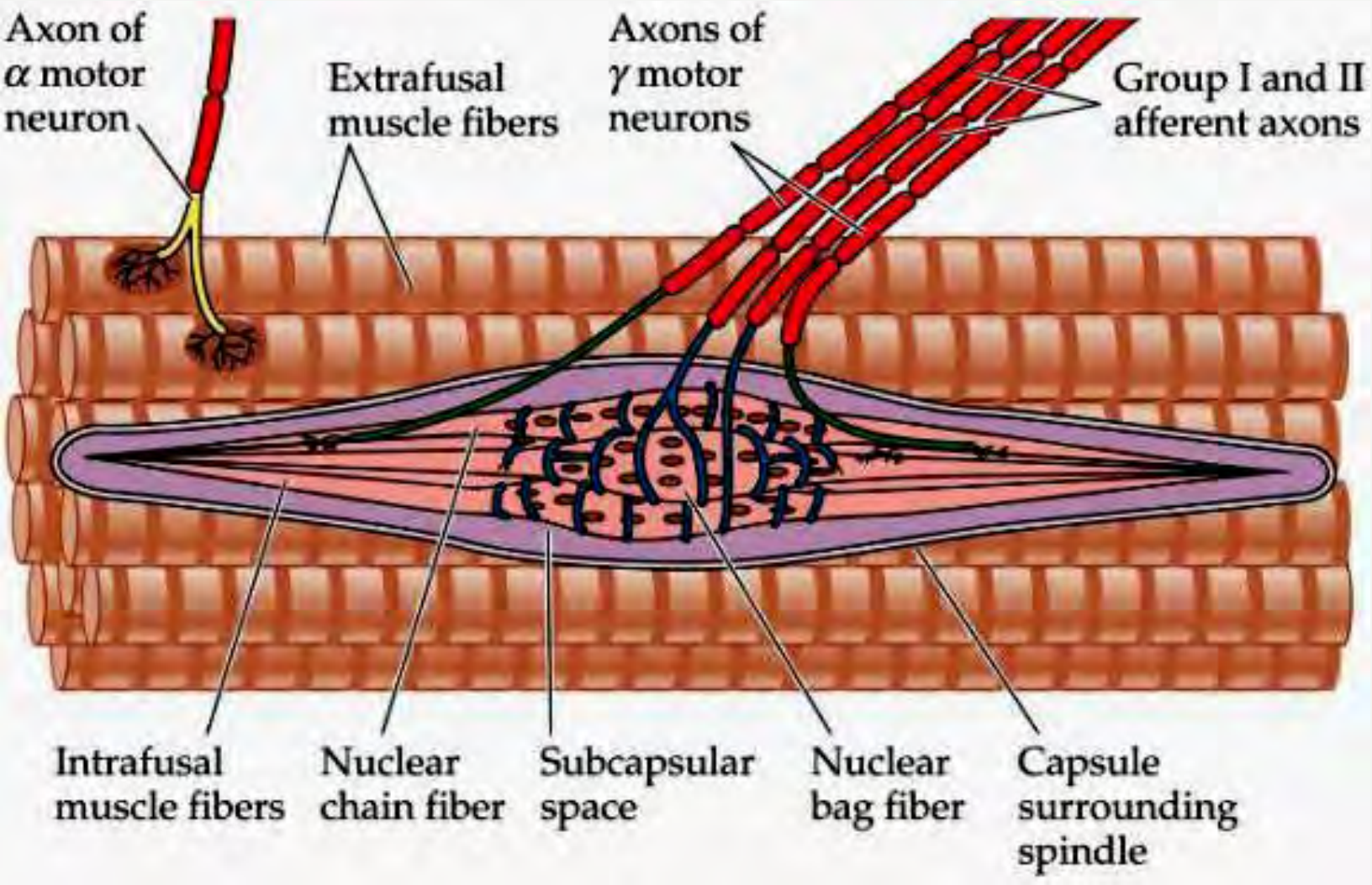
Muscle Spindles are the Principal Proprioceptors



Purves et al., Neuroscience, 4th Ed. (2010)

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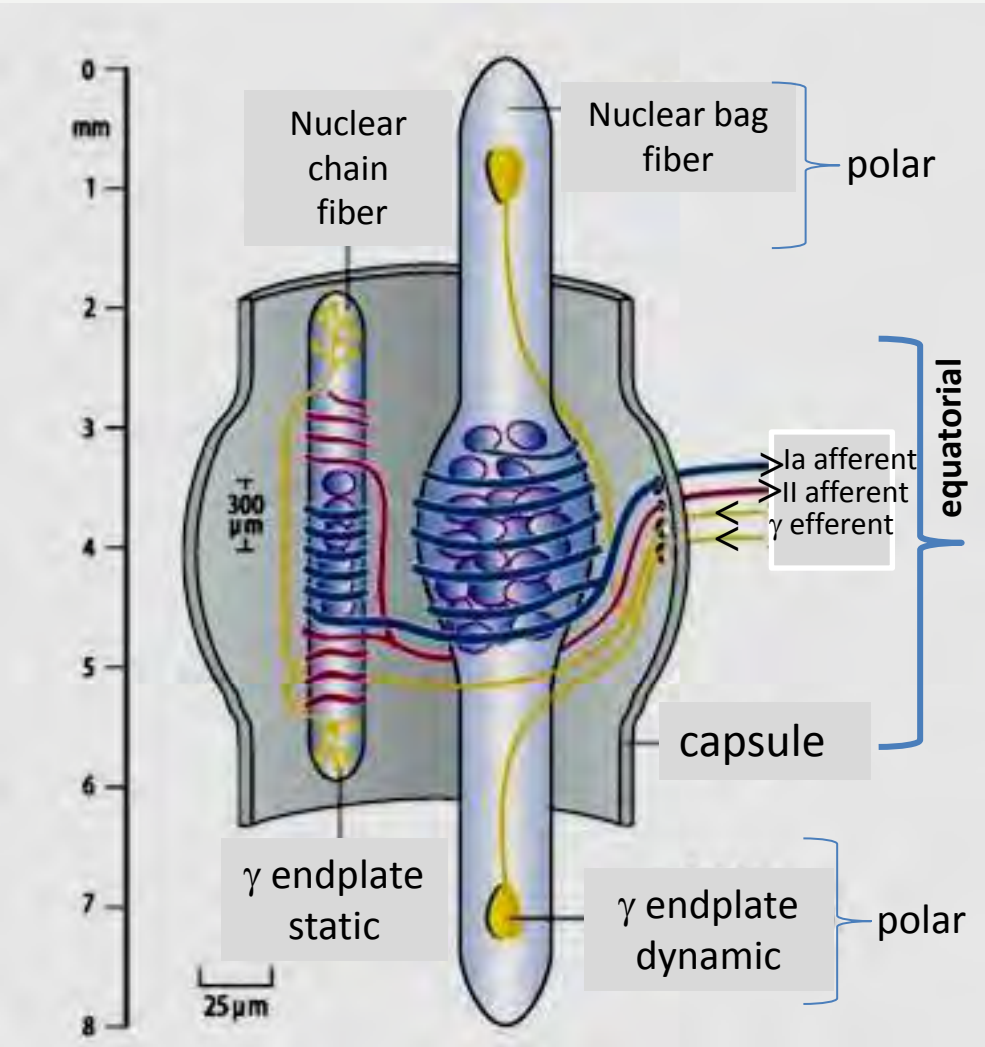
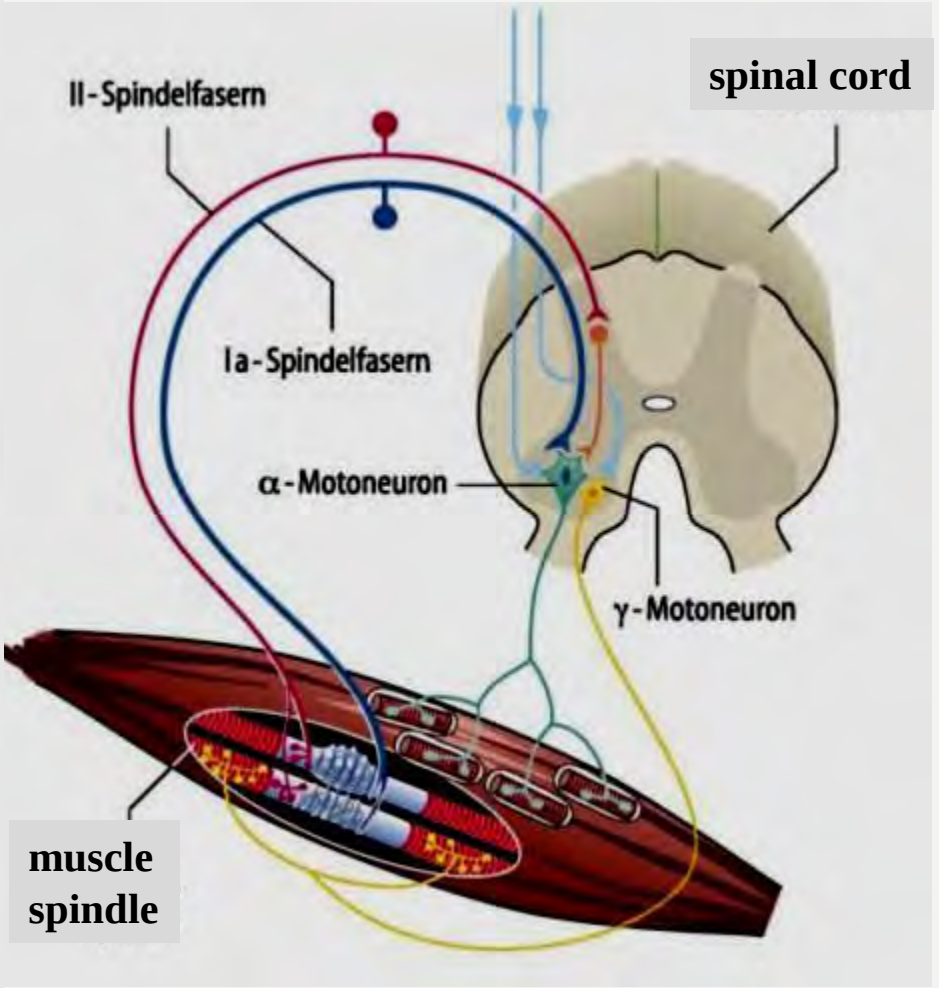
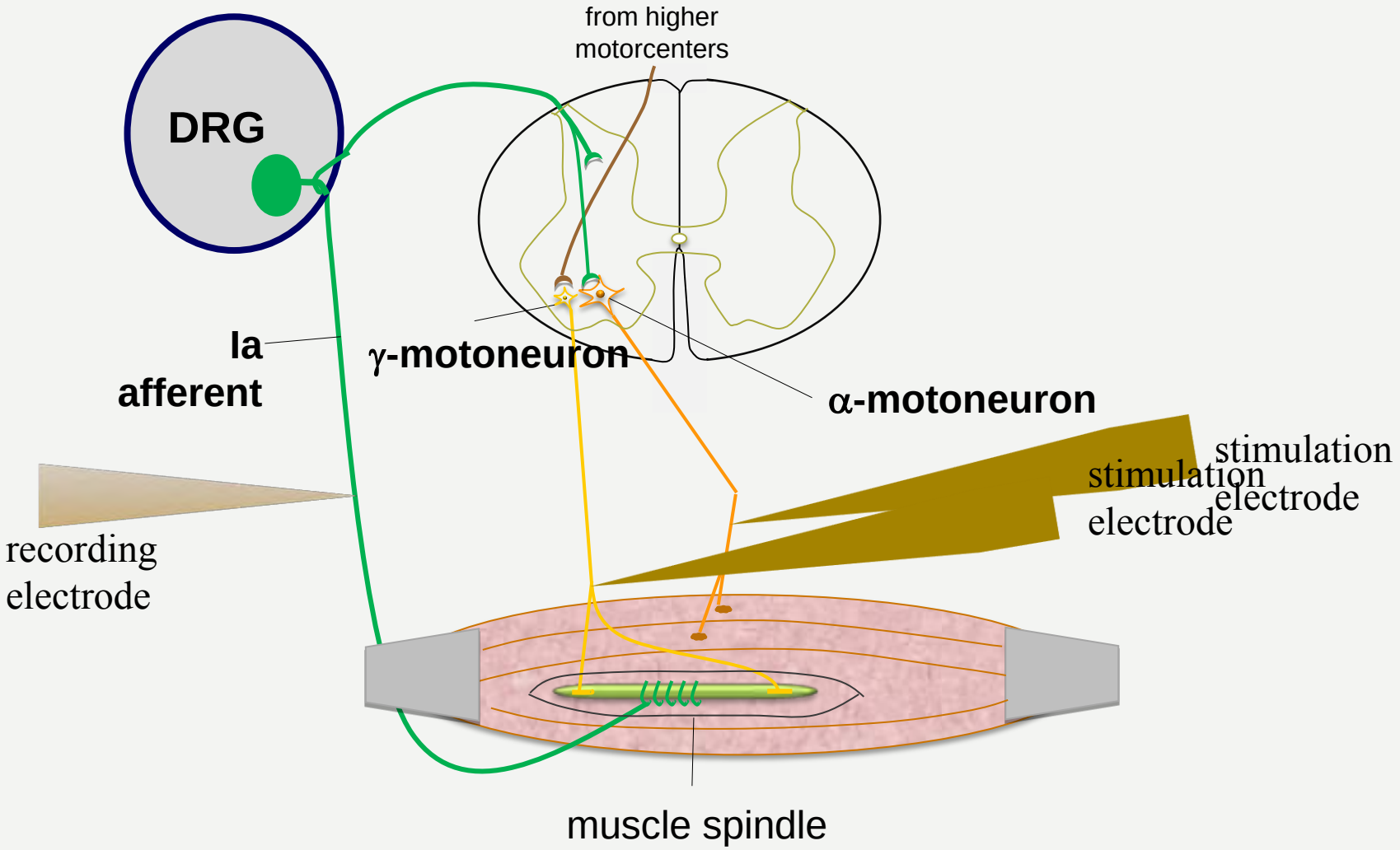


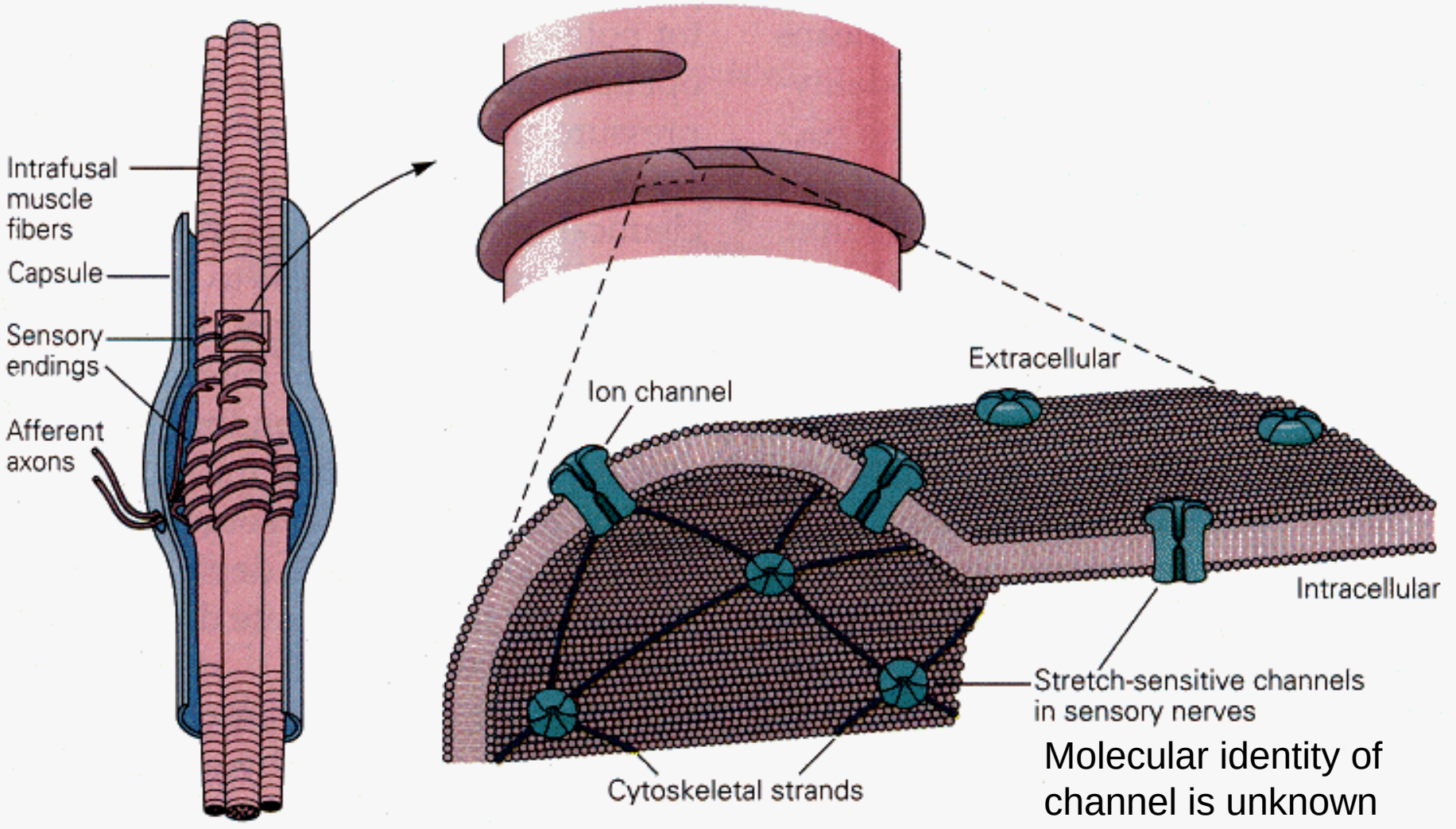


Adapted from Schmidt & Lang, (2007)

Hunt and Kuffler ~1951

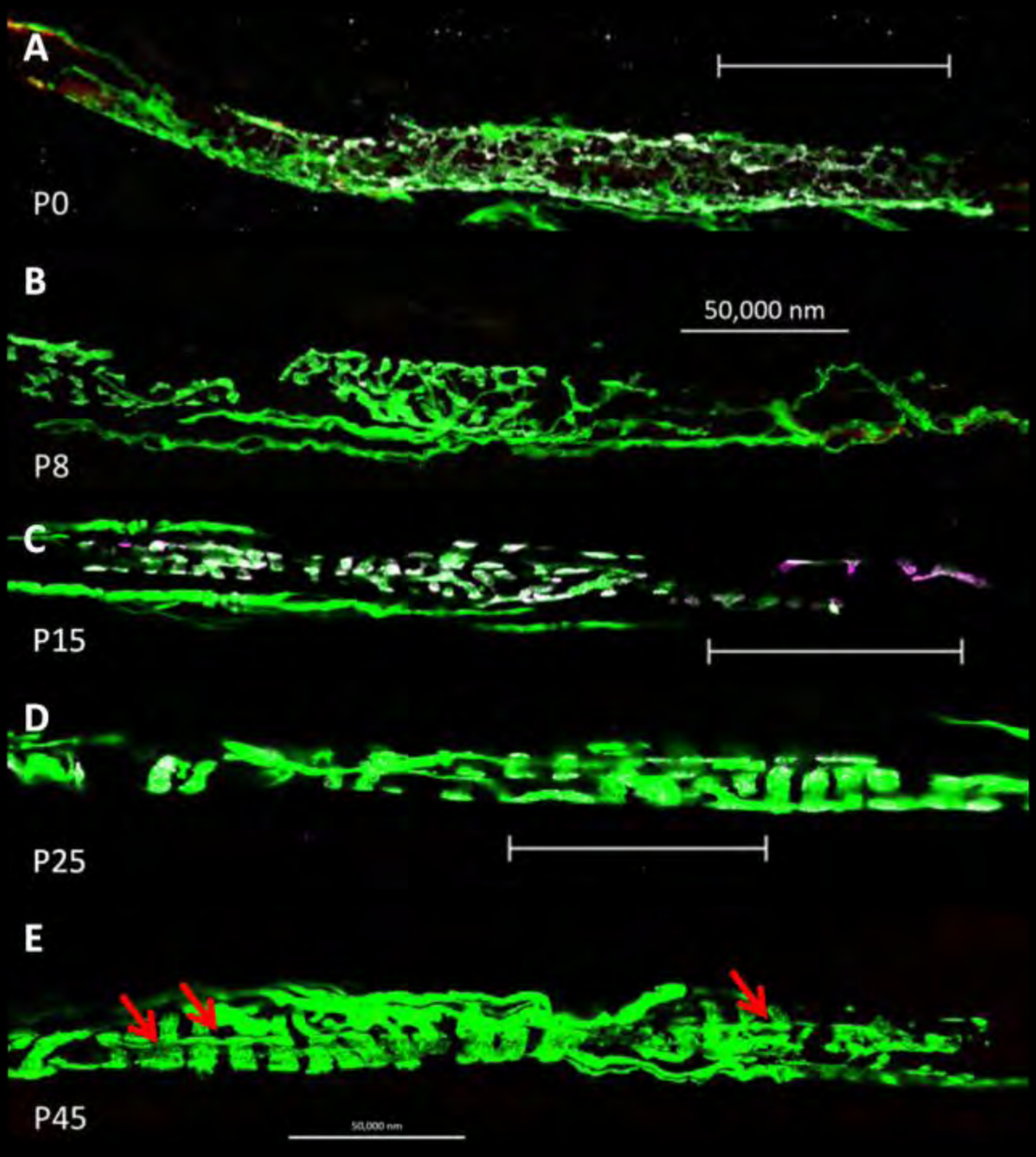


Muscle Spindle Structure



Molecular identity of channel is unknown

Purves et al., Neuroscience, 4th Ed. (2010)


A
P0
B
50,000 nm
P8
C
P15
D
P25
E
P45
50,000 nm

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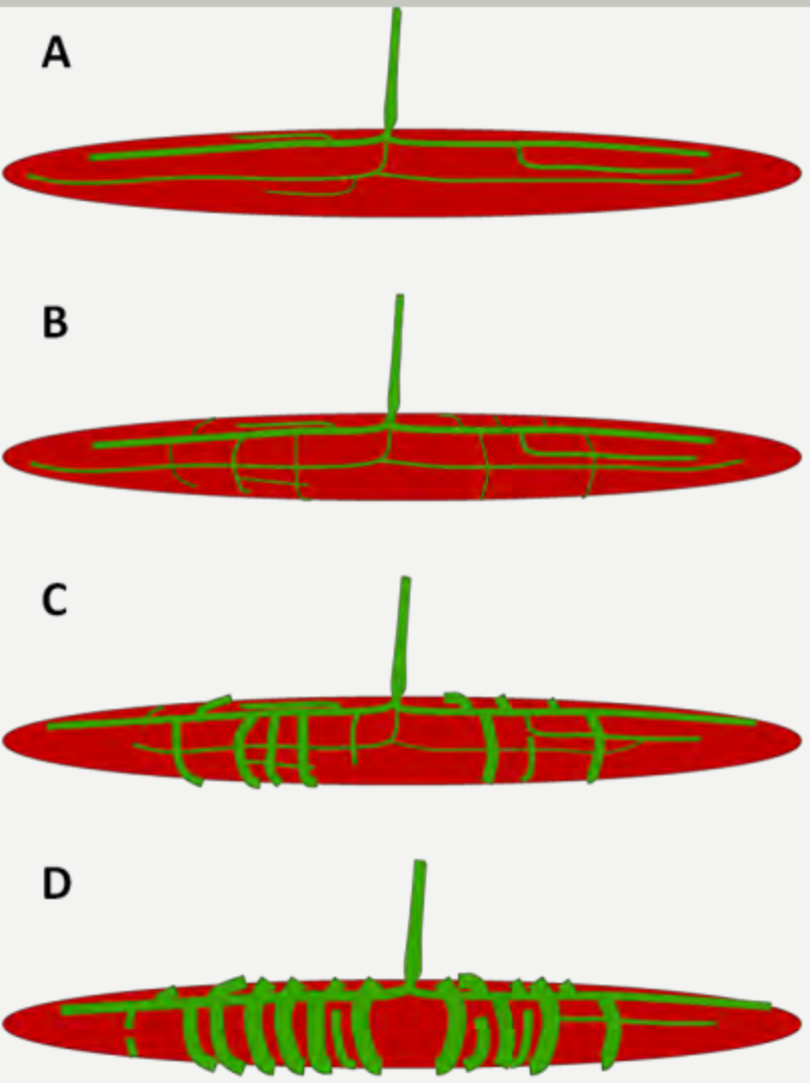
Preliminary Model for Muscle Spindle Development



Age	Morphological Changes
prenatal	sensory nerve contacts myotube, branching starts, creates meshwork
P0 – P15	meshwork; selection of sensory nerve? Branching
P15-P25	thickening of circumferential branches
> P30	regression of longitudinal processes, establishment of annulospiral morphology

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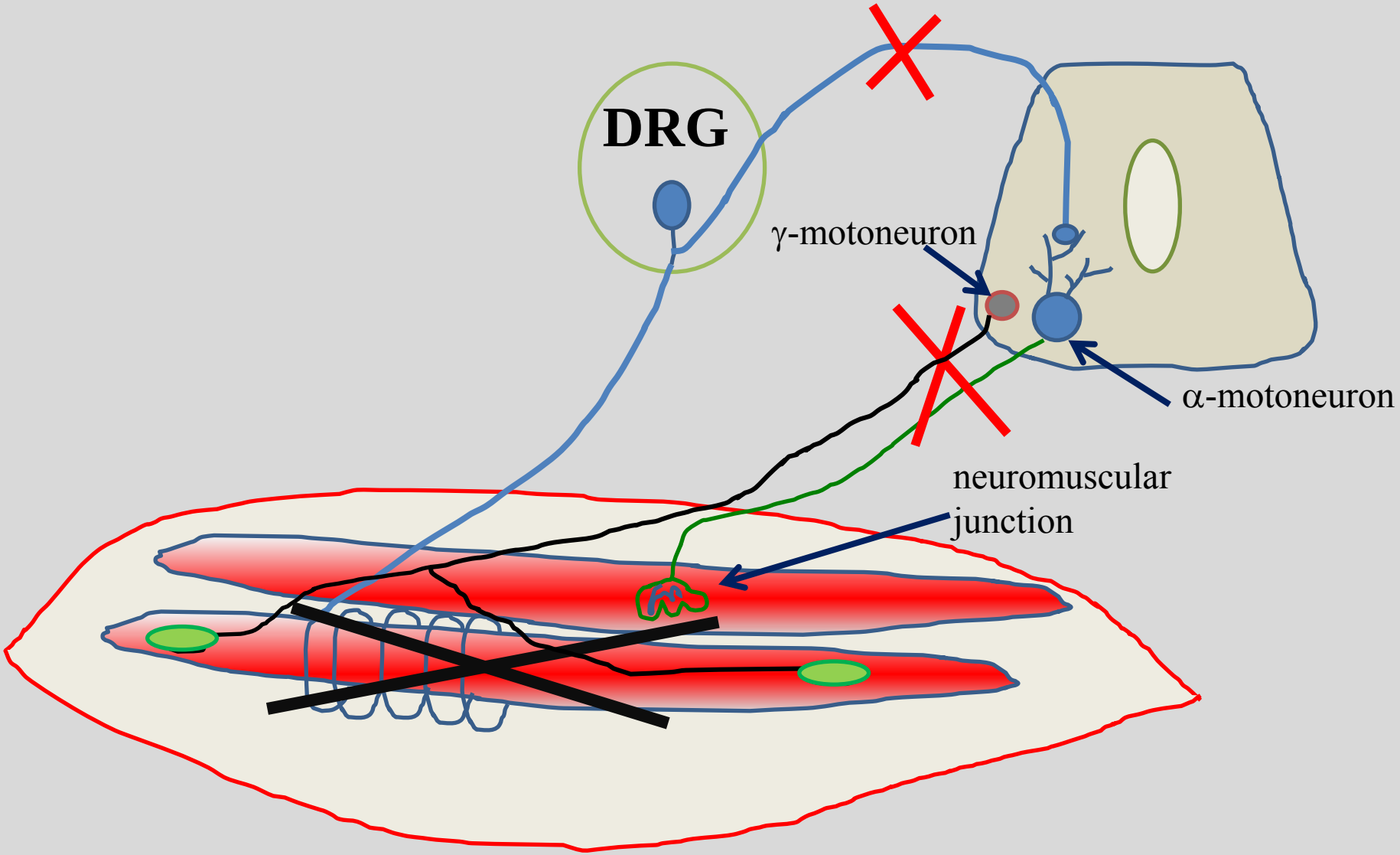
Muscle Spindle II: Molecular Determinants in Muscle Spindle Development

Muscle Spindle Development: Surgical Manipulations

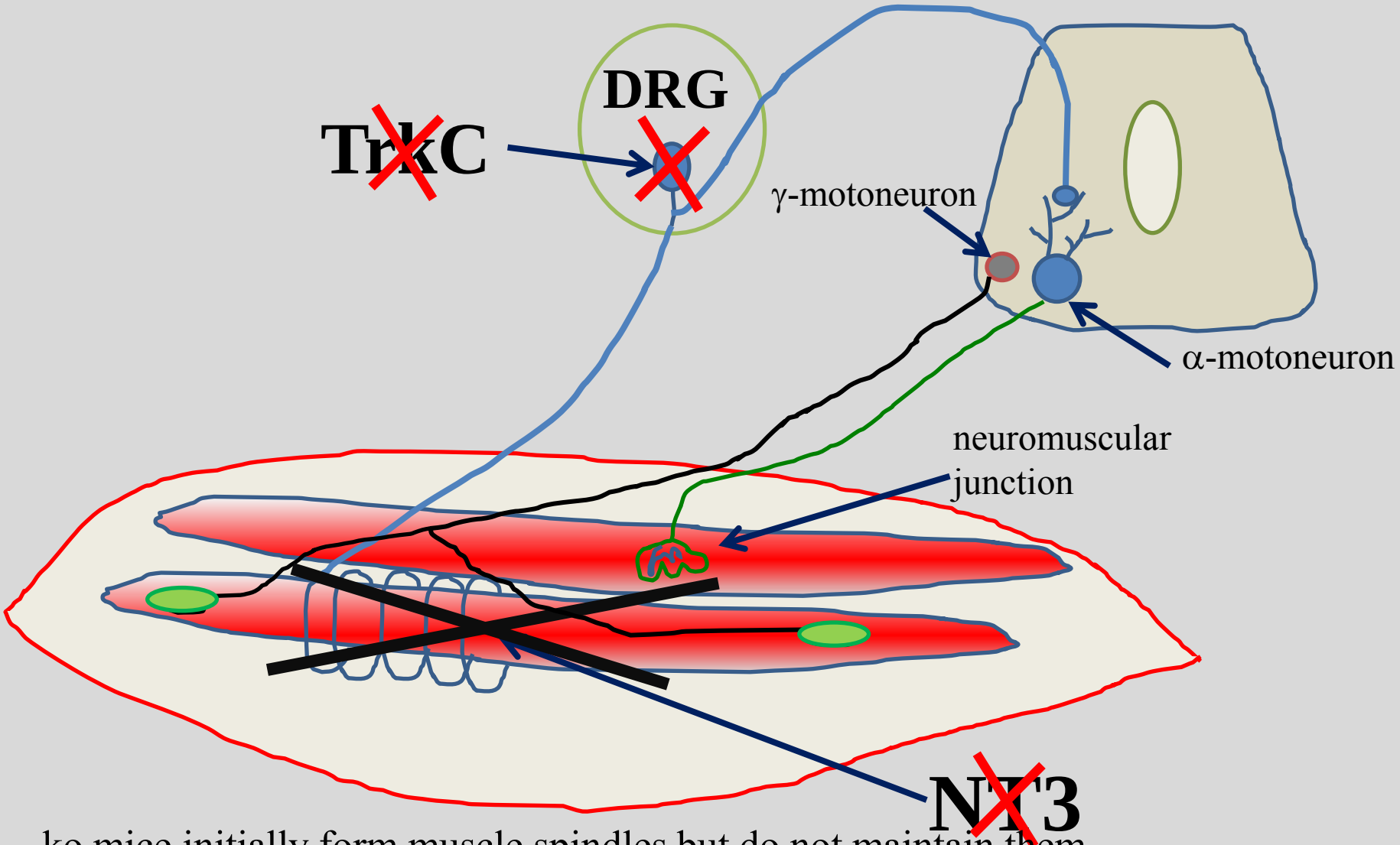
- surgical manipulation at early postnatal stage (at birth)
- Elimination of motor input (Kucera and Walro, 1992) – no effect on the initial differentiation of muscle spindles.
- Elimination of sensory input (Kucera et al., 1993) – rapid degeneration of muscle spindle
- Conclusion:

  Proprioceptive afferents provide inductive signals required to induce the differentiation of intrafusal muscle fibers from immature myotubes.


DRG
γ-motoneuron
α-motoneuron
neuromuscular
junction

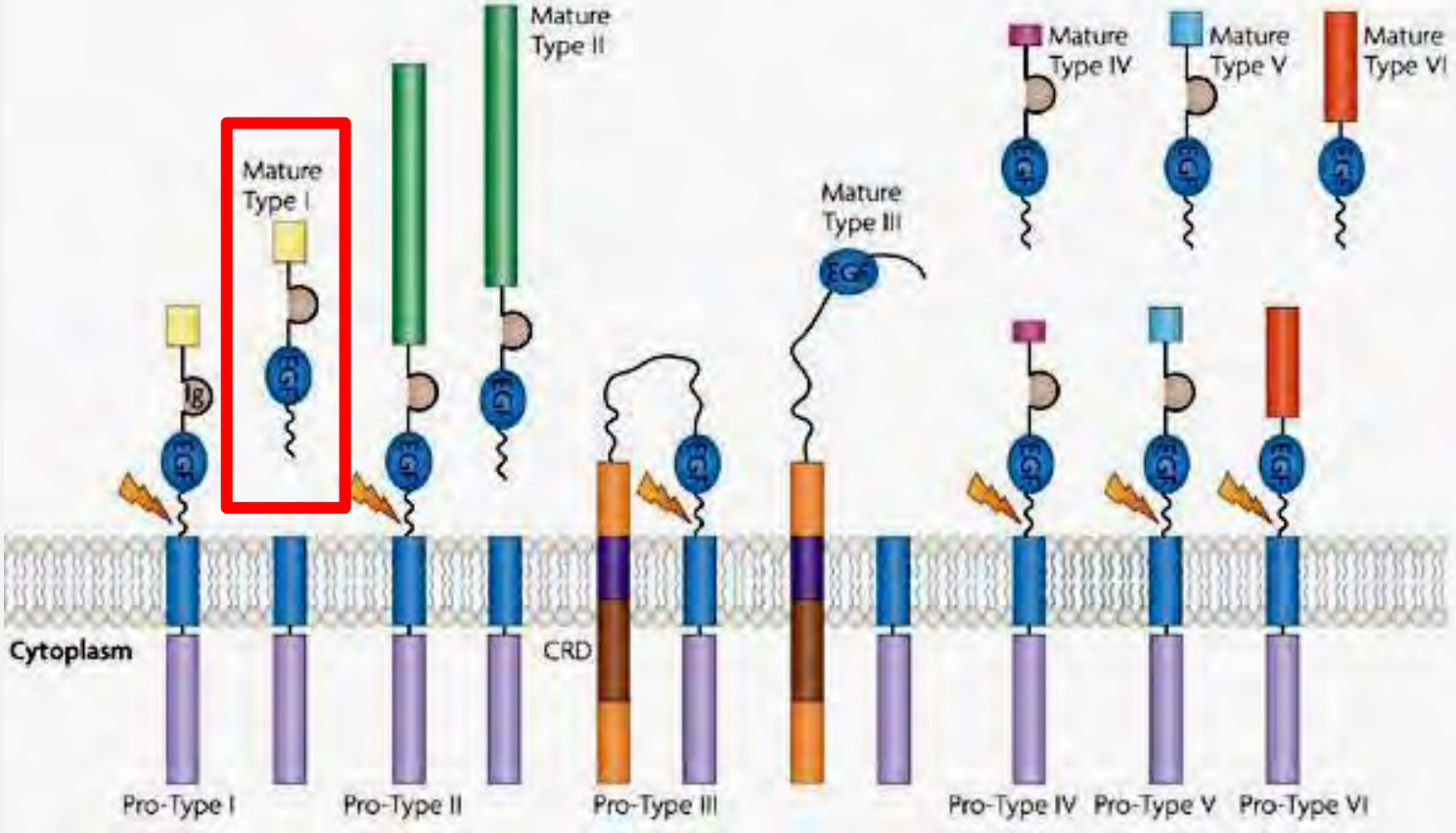
Muscle Spindle Development: The Survival Factors

- Genetic elimination of NT-3 or its receptor tyrosine kinase TrkC results in lack of differentiation of proprioceptive neurons (Klein et al., 1994; Ernfors et al., 1994)
- Injection of antibodies against NT3 into peripheral tissue causes decrease in number of proprioceptive neurons (Oakley et al., 1995).
- Transgenic mice overexpressing NT3 under muscle-specific promotor increases number of proprioceptive afferents and muscle spindles (Wright et al., 1997).
- Neurotrophic factor NT-3 via its receptor TrkC synthesized from target tissue (intrafusal fiber) ensures survival of proprioceptive neuron!



- ko mice initially form muscle spindles but do not maintain them
- Survival factor NT3 and its receptor TrkC – retrograde transport of NT3
- What is the inductive signal from the Ia afferent that induces intrafusal fiber differentiation?

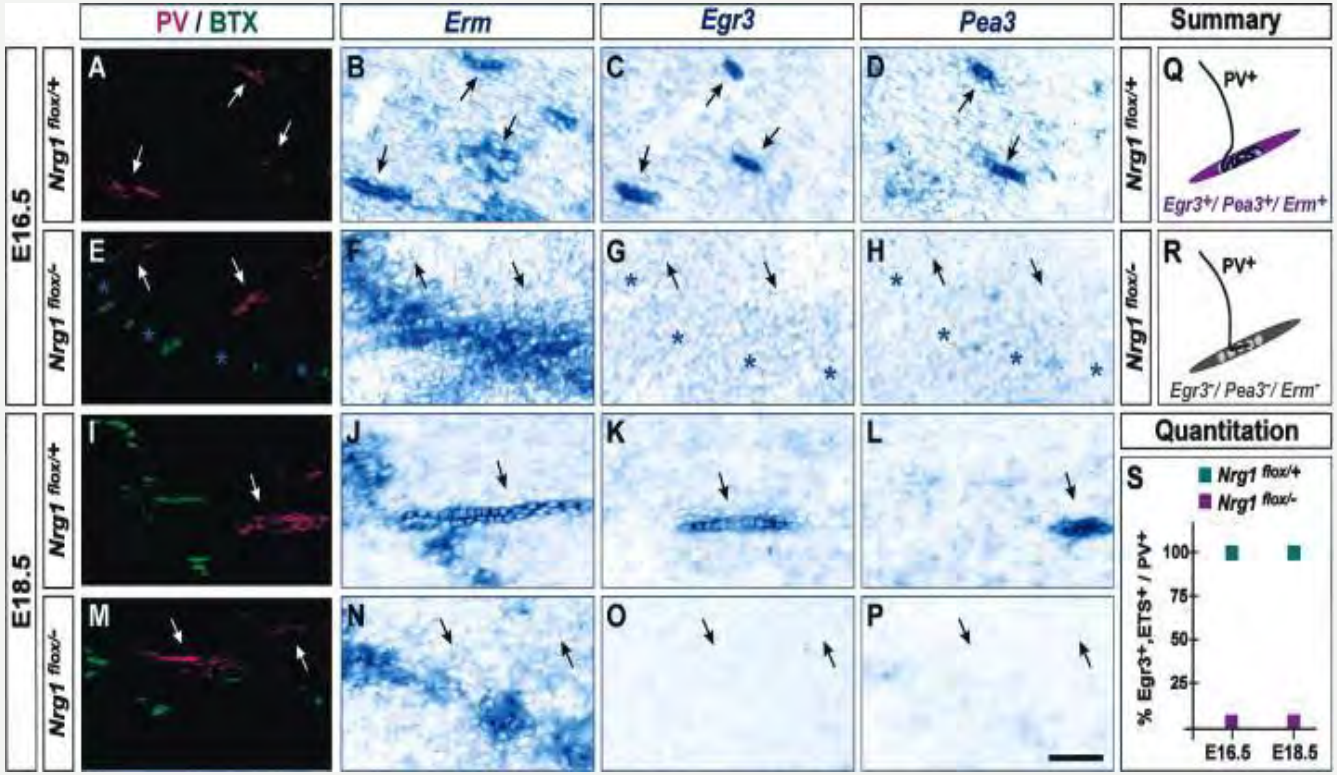
Role of NRG-1 and the ErbB 2/3 Receptor in Spindle Development



- CRD-Nrg-1 and Ig-Nrg-1
- Ig-Nrg-1 preferentially expressed by proprioceptive neurons in DRG; CRD-Nrg-1 expressed by most neurons in DRG; ARIA: Ig-Nrg-1

Mei and Xiong (2008) Nature Rev. Neurosci. **9:** 437-452

Effect of Nrg-1 Deletion



- Initial differentiation of proprioceptive neurons is not affected in Isl1-Cre Nrg-1$^{flox/flox}$ mice
- However, no differentiation of muscle spindles

Hippenmeyer et al., 2002

ErbB2 ko Mice

ErbB2flox/flox MCK-Cre mice have altered gait, problems in motor coordination

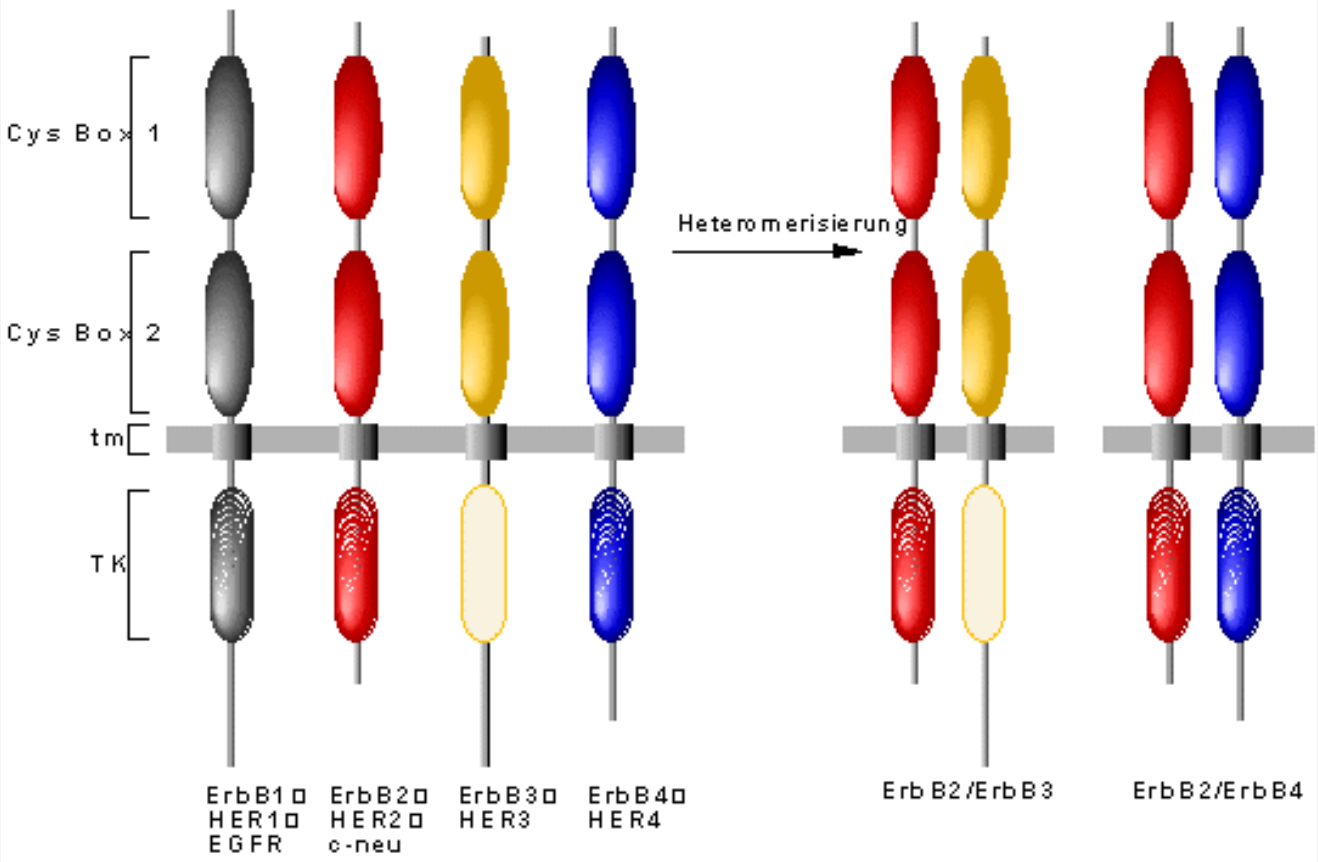
Mice maintain limbs in abnormal position – progressing from flexor to extensor posture

During walking, mice rotate foot, leg contacts ground

- Muscle spindles are absent in mice – NMJs are normal only slightly fragmented

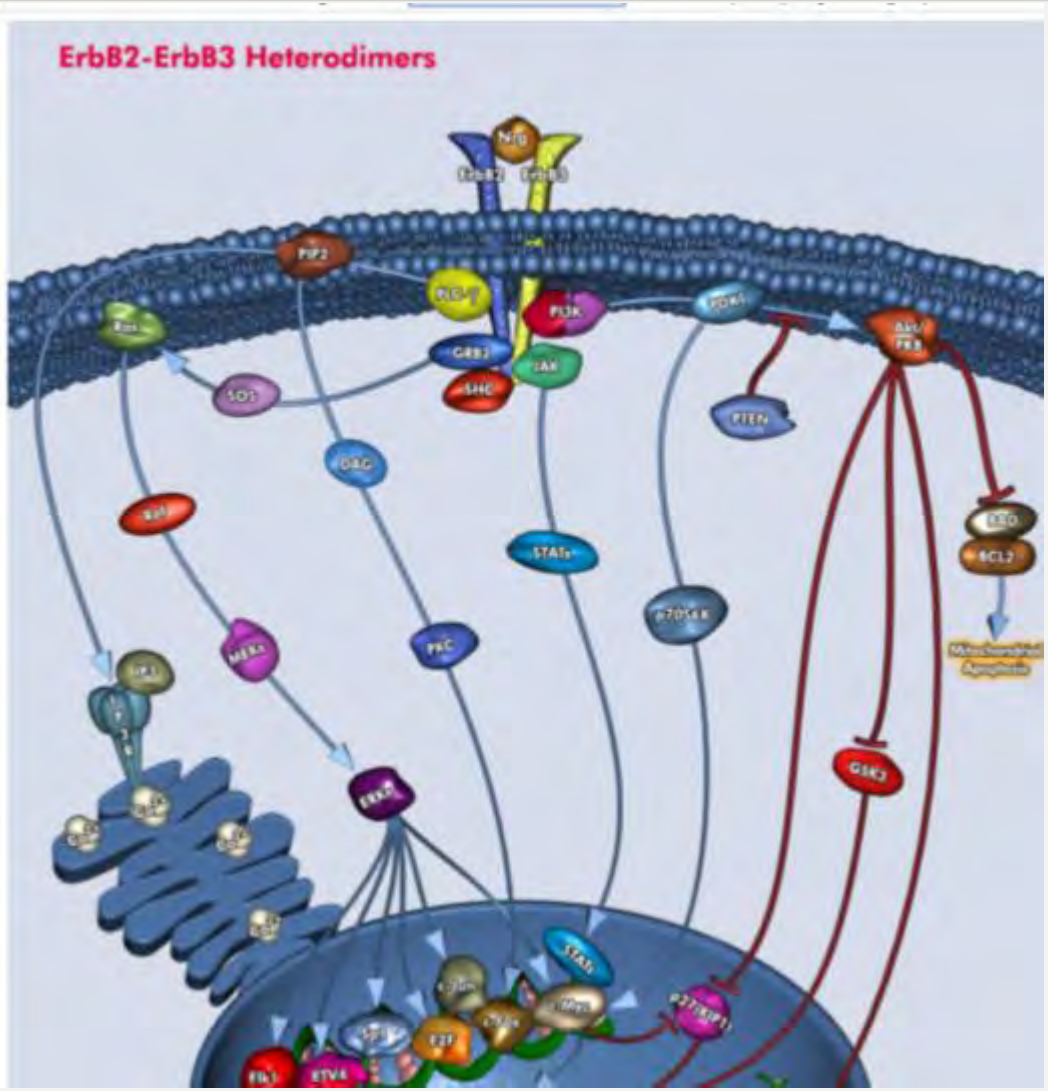
Andrechek et al., 2002; Leu et al., 2003;

The ErbB Receptor Family



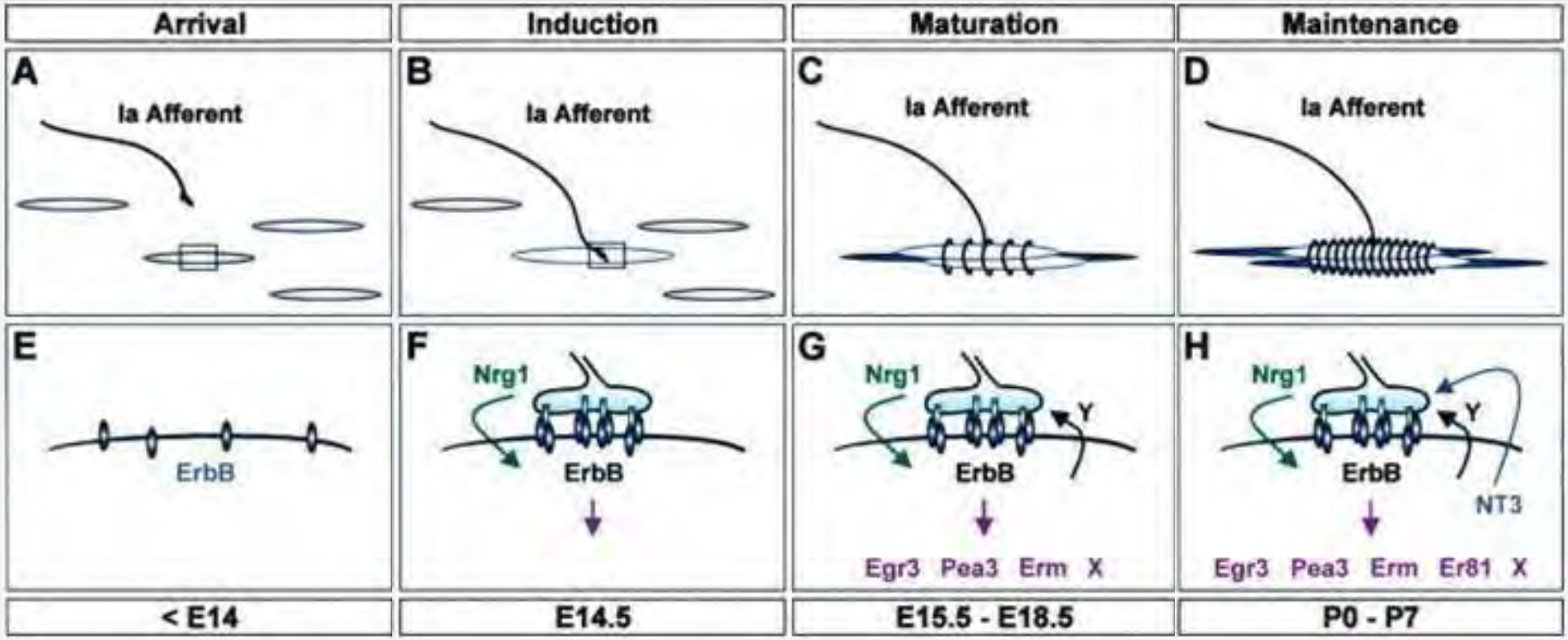
- There are 4 members of the ErbB tyrosine kinase receptors, the EGF-receptor (ErbB1, HER1), ErbB2 (HER2, Neu), ErbB3 (HER3) and ErbB4 (HER4).
- All form homodimers and ErbB2 forms heterodimers with ErbB3 and ErbB4

The ErbB Receptor Family



- No specific ligand for ErbB2 identified
- More likely that ErbB2 is a coreceptor for ligands that bind to ErbB3, ErbB4 or EGFR

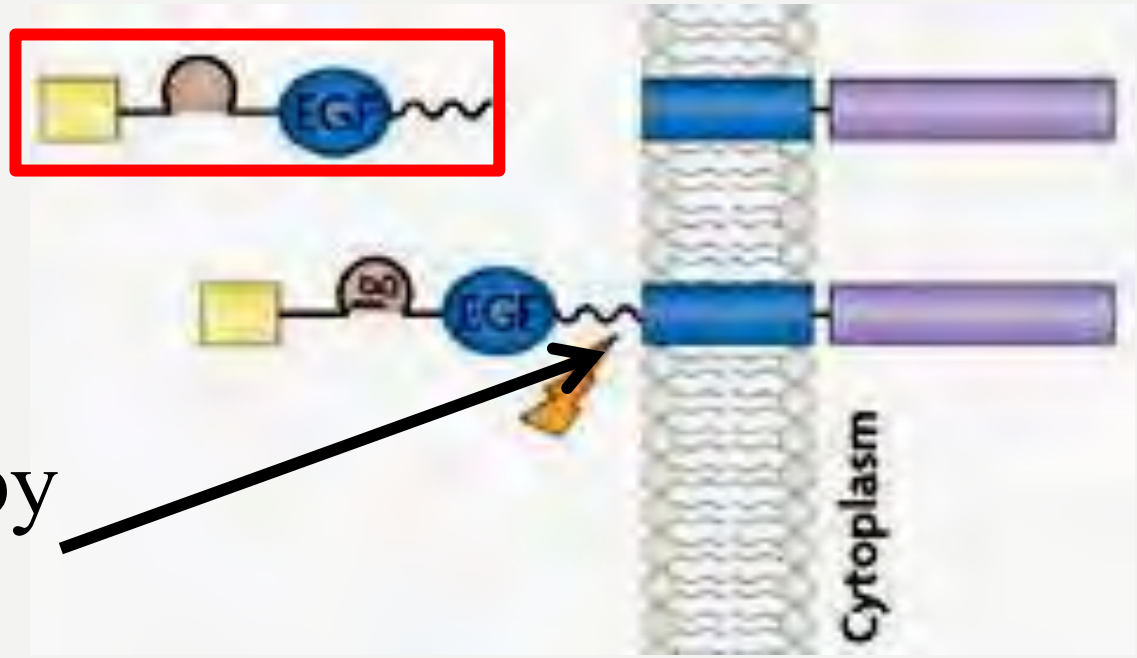
Role of NRG-1 and the ErbB 2/3 receptor in spindle development



- Ia afferent-derived Nrg-1 binds to ErbB2 receptor on myotube precursor membrane
- Induces a signaling cascade which will activate genes coding for transcription factors (*Egr3*, *Pea3*, *Erm*) that are selective for intrafusal fibers
- Transcription factors activate transcription cascade leading to differentiation of intrafusal fibers
- Transcription factors induce synthesis of NT-3 which will ensure survival of proprioceptive neuron by binding to its TrkC receptor

Hippenmeyer et al., 2002

Role of NRG-1 and the ErbB 2/3 Receptor in Spindle Development

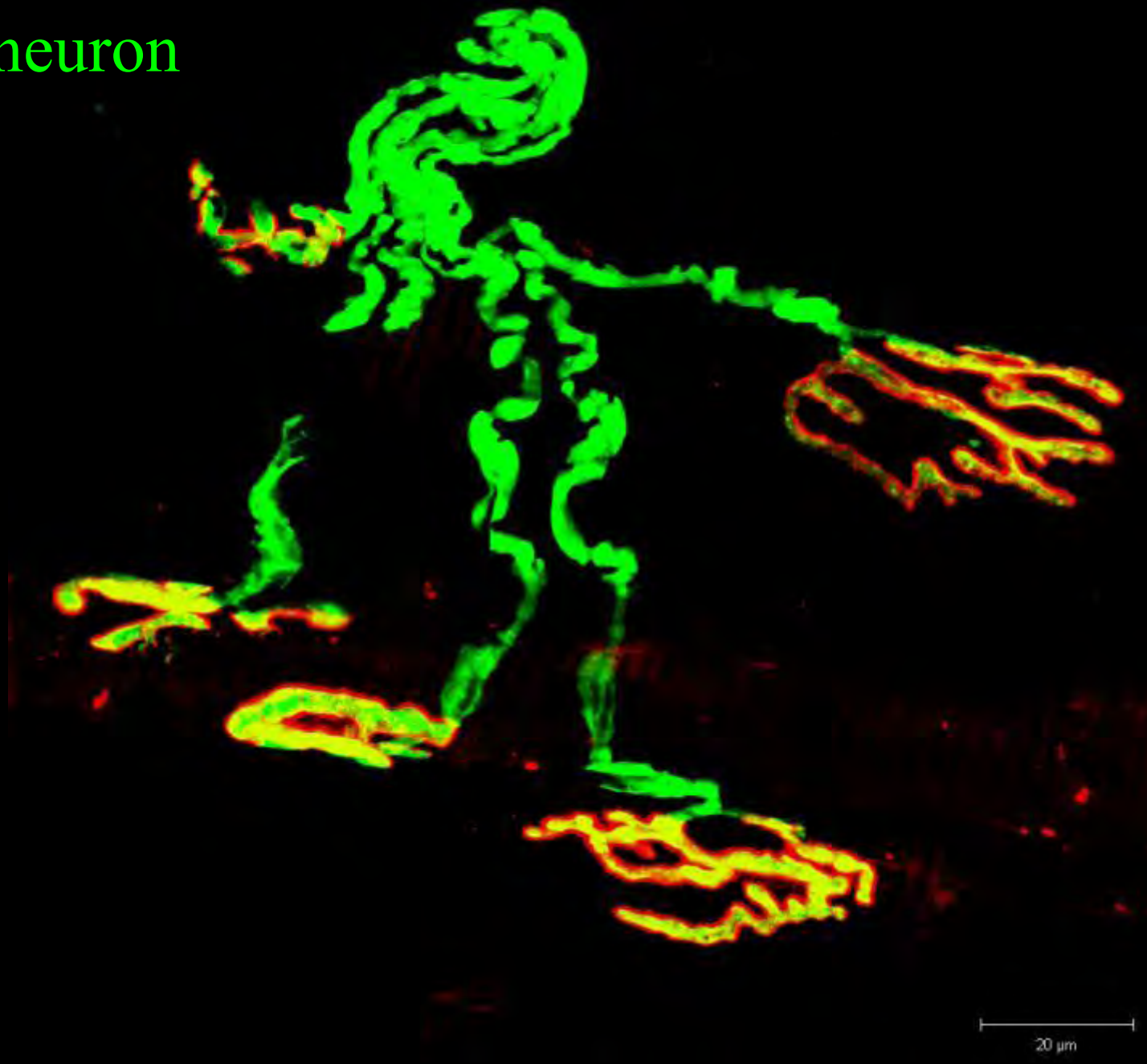


Cleavage by BACE

- Ig-Nrg-1 preferentially expressed by proprioceptive neurons in DRG; ARIA: Ig-Nrg-1
- Ig-Nrg-1 cleaved by BACE (= β-secretase)

red: AChR

green: motoneuron



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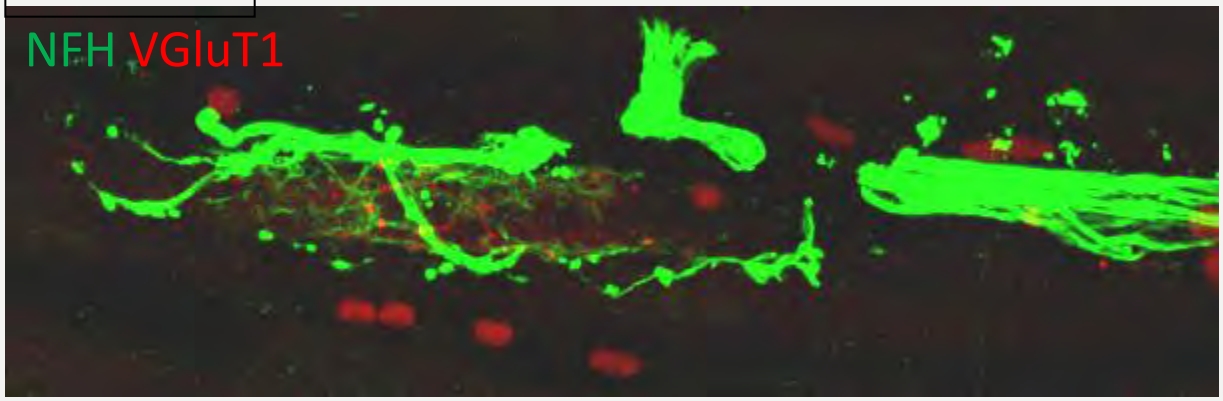
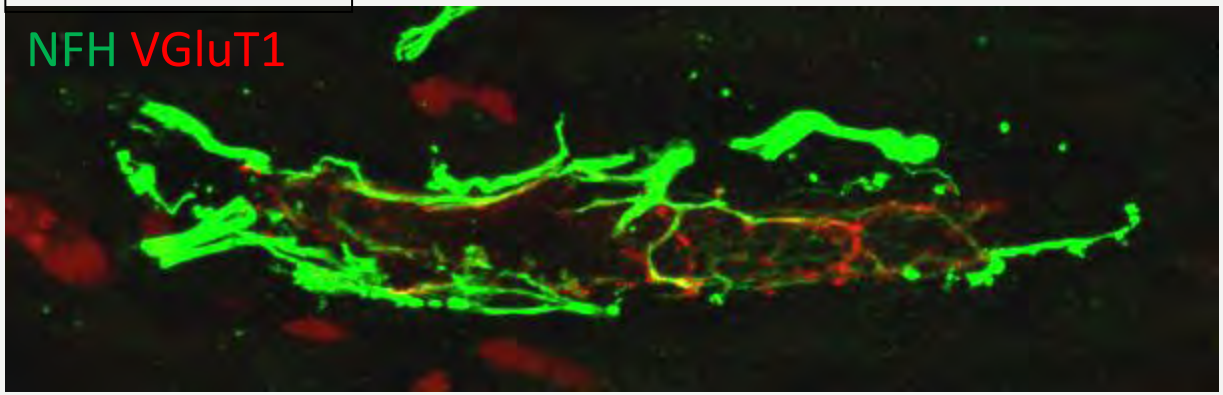
No Changes at Annulospiral Endings of Agrin ko Mice

WT mouse



agrin -/- mouse



20µm

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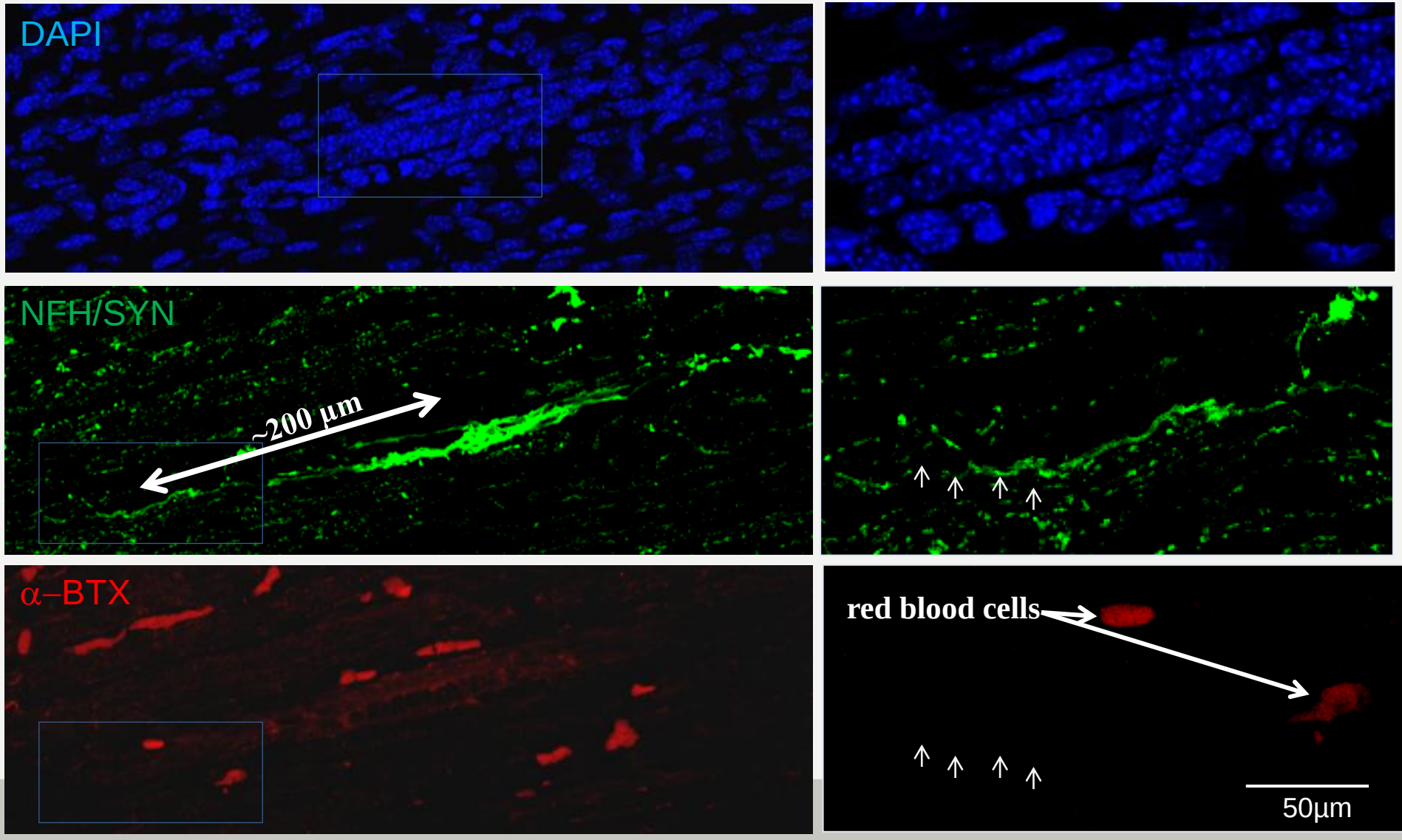
No AChR Aggregates at γ-MN Endplates in Agrin -/- Mice



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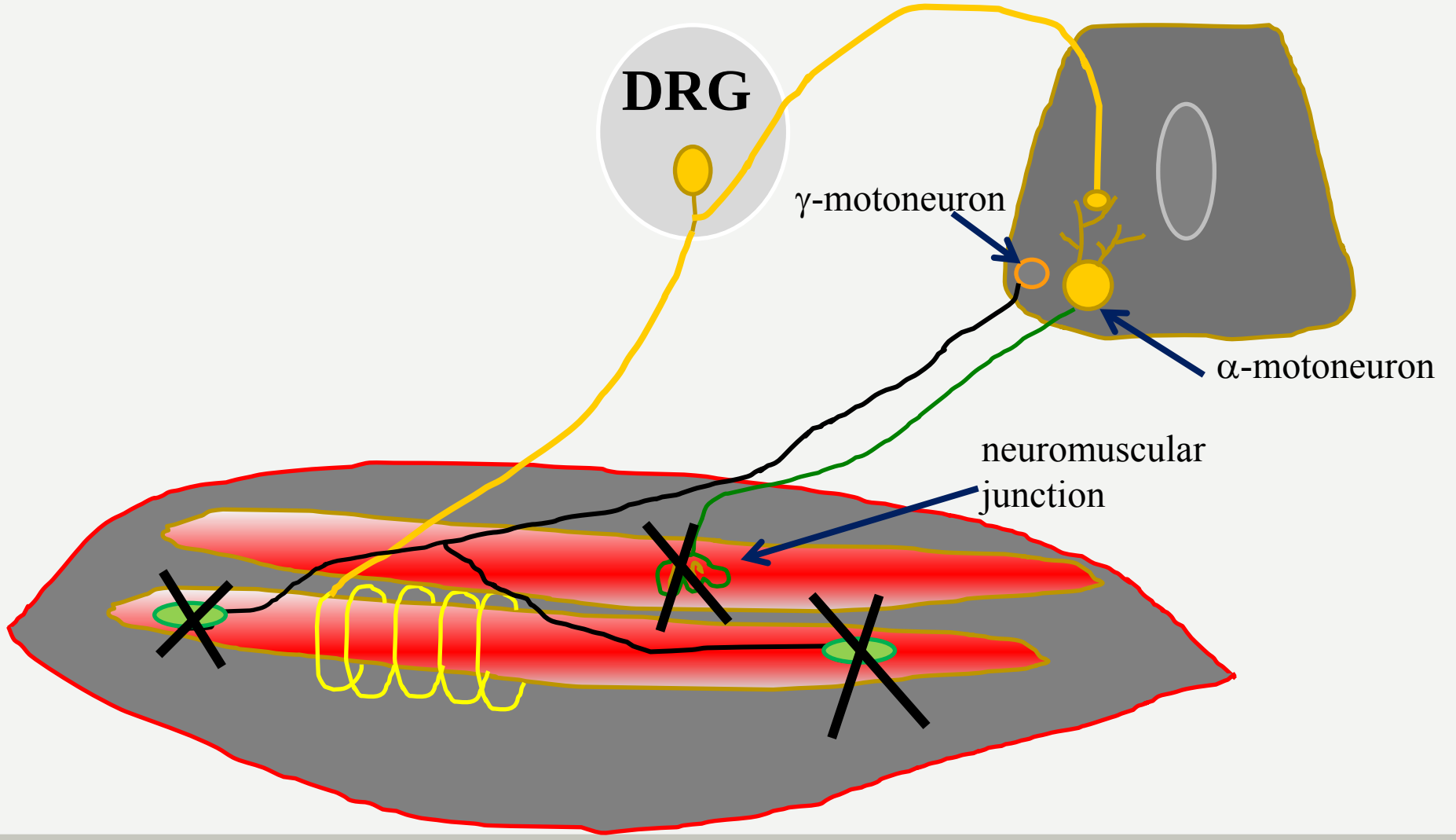
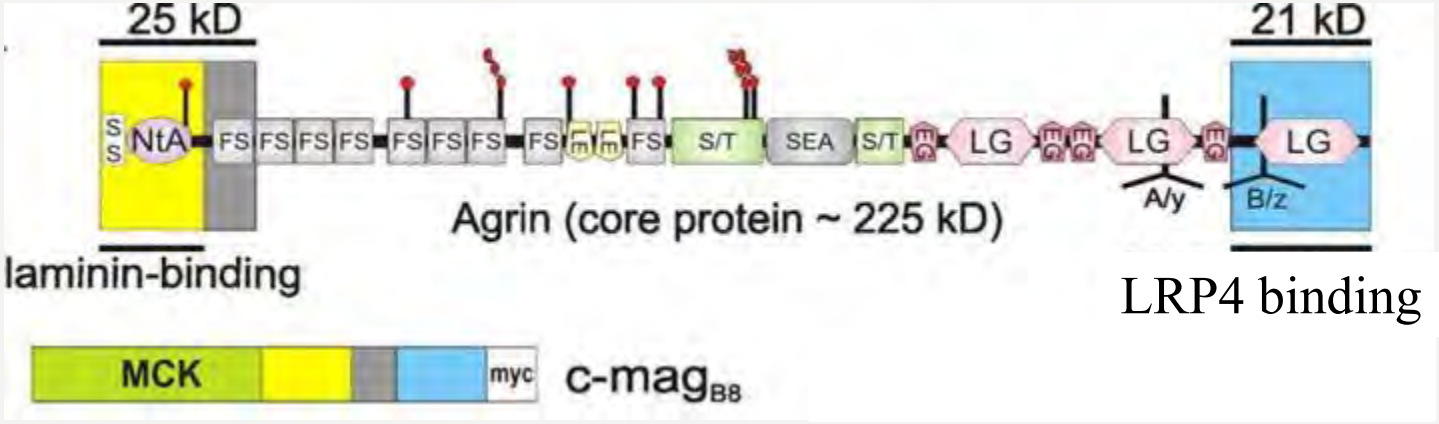
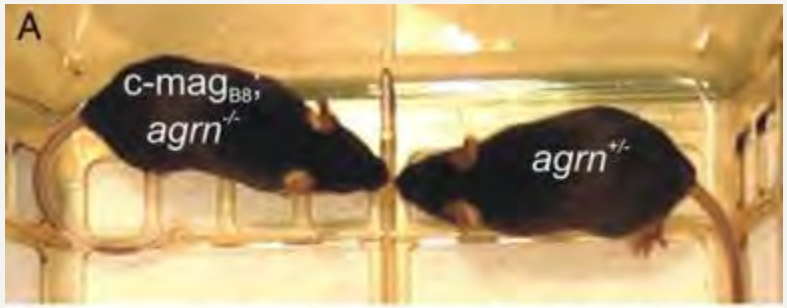
E18 Agrin ko Mice



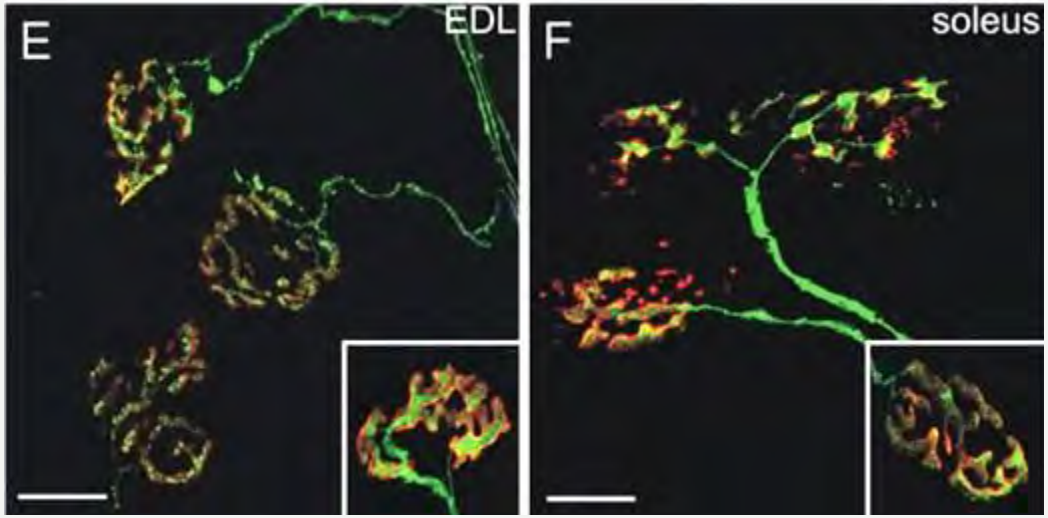
Rescue of Agrin -/- Mice by Muscle-Specific Expression of Miniagrin





B

line	born	fertile	mice died <3 mo.	age reached
c-mag$_{B8}$; *agrn*$^{-/-}$	60	yes	5%	9 mo.
m-mag$_{z8}$_*H*; *agrn*$^{-/-}$	15	yes	0	>12 mo.
m-mag$_{z8}$_*L*; *agrn*$^{-/-}$	18	yes	12%	>12 mo.



Lin et al. PNAS 2008

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Muscle-Specific Reexpression of Miniagrin Rescues γ-MN Endplates