Impact of neuregulin 1 type III overexpression on motor axon development in spinal muscular atrophy mice

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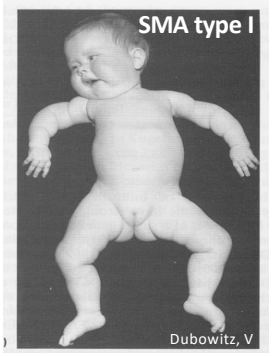
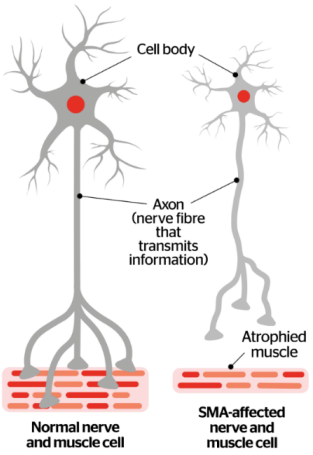
Impaired motor axon development *in utero* is associated with rapid postnatal degeneration in spinal muscular atrophy (SMA)

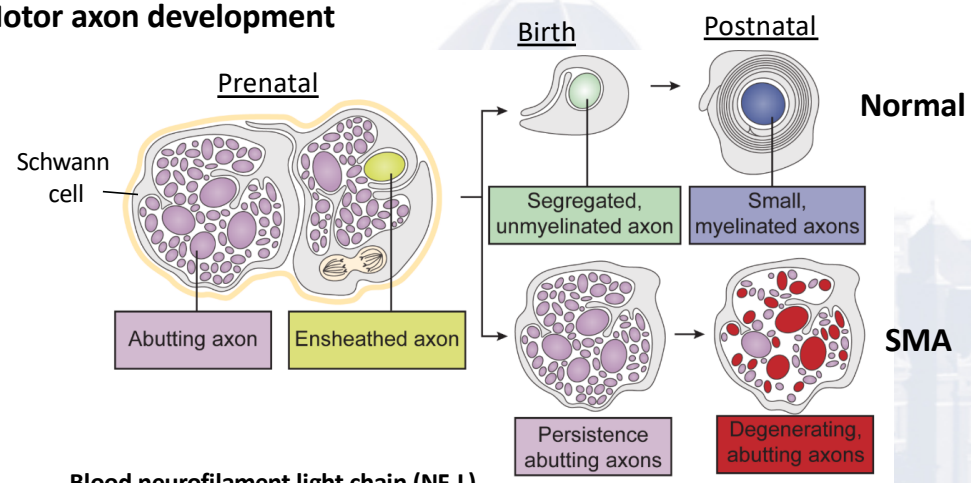
Spinal Muscular Atrophy (SMA)

- Autosomal recessive, early onset motor neuron disease
- Leading inherited cause of infant and childhood mortality
- 3 gene targeted treatments FDA approved in last 5 years:
  - AAV9-*SMN* gene therapy: onaemnogene abeparvovec-xioi
  - *SMN2* splicing modulation: ASO (nusinersen), small molecule (risdiplam).
- Therapeutic efficacy variable. Combinatorial treatments are needed.
- Limited insight regarding molecular and cellular pathogenesis of SMA limits novel therapeutic target identification.

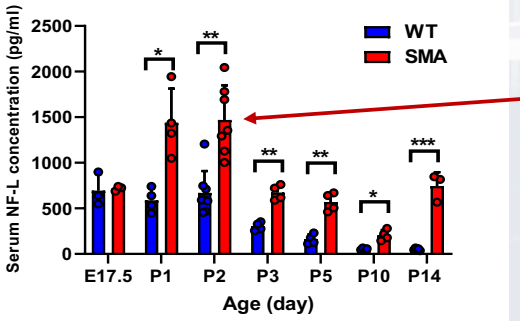




Motor axon development



Blood neurofilament light chain (NF-L)



Slowed development of SMA motor axons is associated with rapid degeneration and early release of NFL into blood

Kong et al. Sci. Transl. Med., 2021

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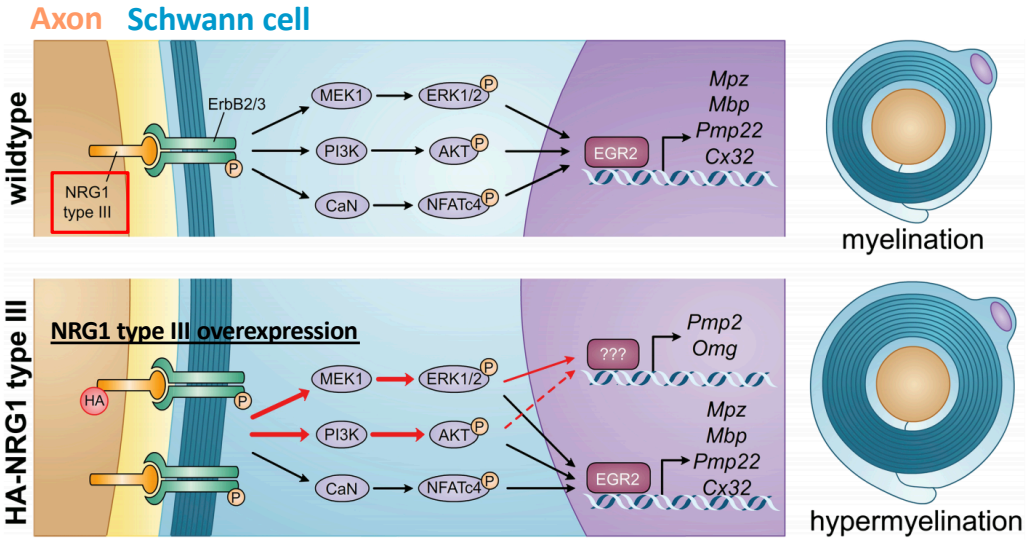
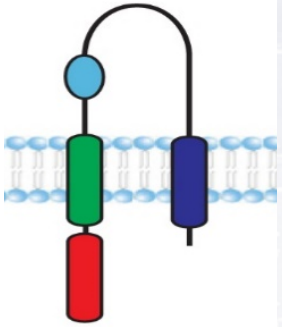
NRG1 type III-ErbB2/3 signaling mediates axon-Schwann cell interactions during development and is reduced in SMA tissues



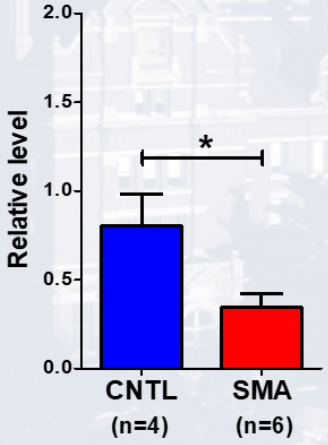
Belin et al. Hum. Mol. Gen., 2018.

NRG1 type III levels are reduced in human and mouse neural tissues

NRG1 type III



NRG1-III (human spinal cord)



Biological roles:

- Axon ensheathment
- Myelination

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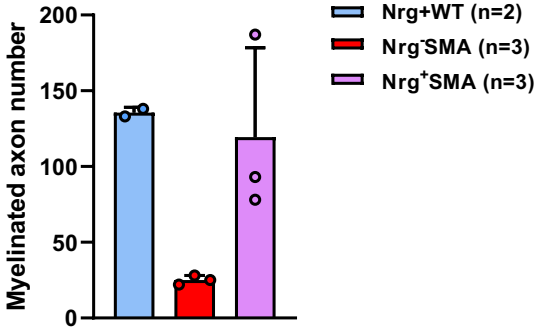
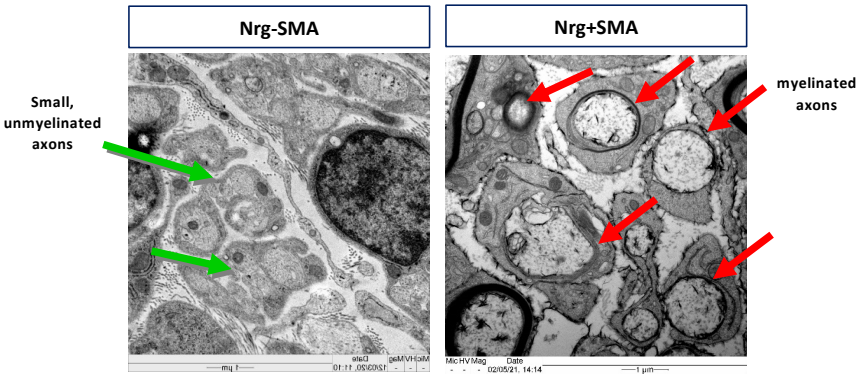
NRG1-III overexpression in neurons hastens motor axon myelination and increases myelin thickness in SMA mice

SMAΔ7 mice x Thy1-HA-NRG1-III mice

Postnatal day 2 (P2) – early symptomatic time point

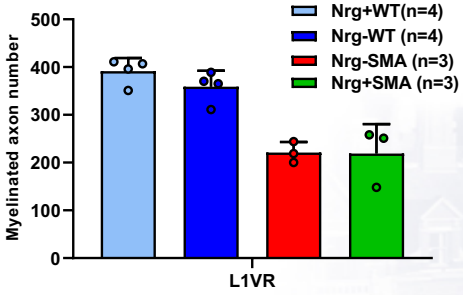
Myelinated motor axon number



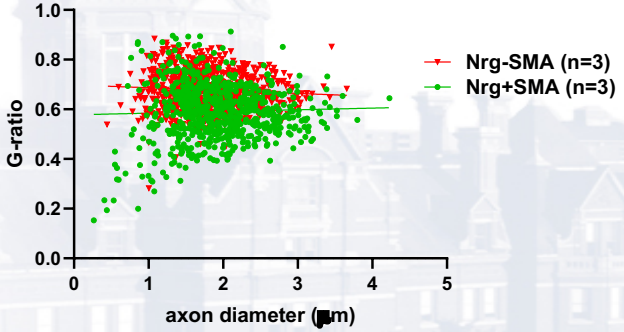


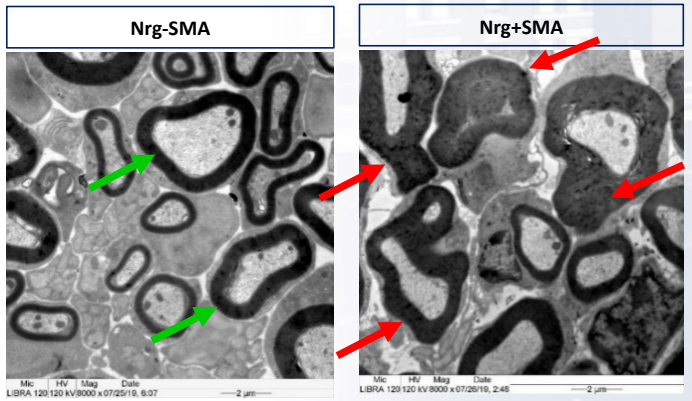
P14 – late symptomatic time point

Myelinated motor axon number



G-Ratio and axon diameter





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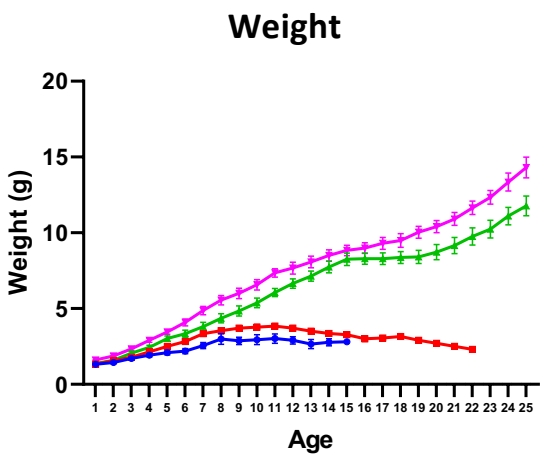
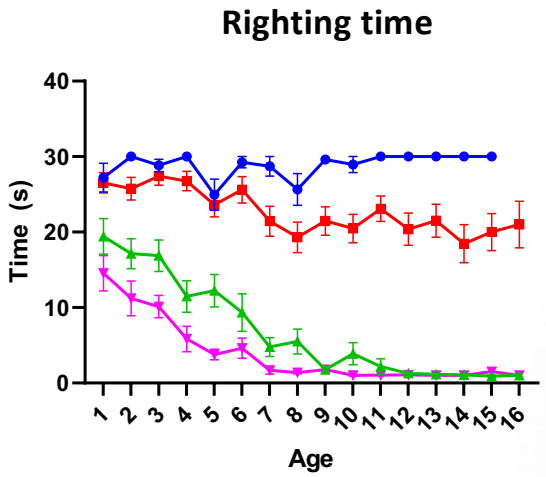
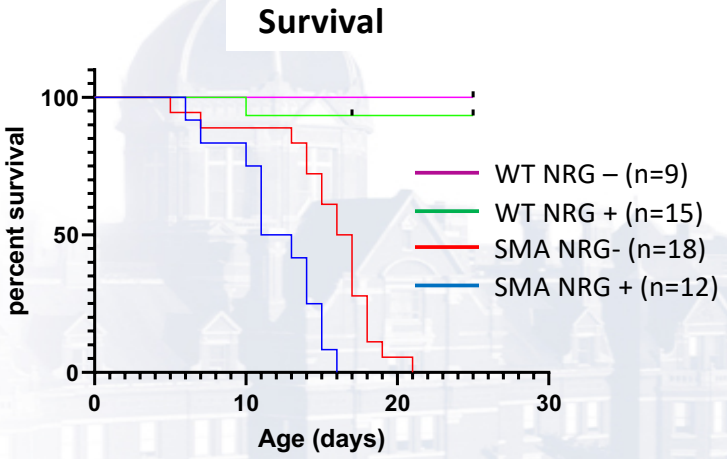
NRG1-III overexpression does not improve motor behavior or survival of SMA mice







Conclusions

- Impaired SMA motor axon radial growth and Schwann cell ensheathment begin *in utero*.
- Those SMA motor axons that are most developmentally immature degenerate rapidly postnatally.
- NRG1 type III levels are reduced in human and mouse SMA tissues.
- Overexpression of NRG1 type III hastens SMA motor axon myelination and motor axon myelin thickness, but does not improve motor behavior or survival of SMA mice.
- These studies suggest that hastening SMA motor axon myelination alone is insufficient to ameliorate the SMA disease phenotype.

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