SMN Deficiency Disrupts Lineage Specification in Human Neuromuscular Organoids Modeling Spinal Muscular Atrophy

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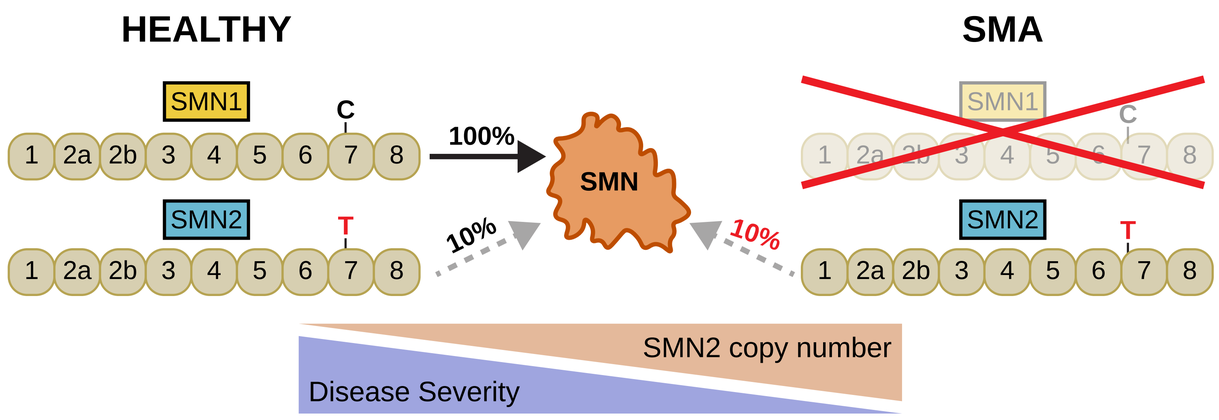
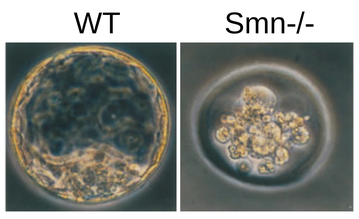
Introduction

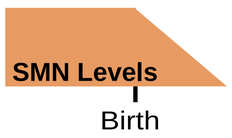
Spinal muscular atrophy (SMA) is an early onset **motor neuron disease** caused by a **deficiency** of **Survival of Motor Neuron (SMN)** protein. SMN is encoded by *SMN1,* and its paralog *SMN2,* in humans. These two differ in a single nucleotide in exon 7. As a result, while all transcripts of *SMN1* are translated into functional, full-length SMN protein, approximately 90% of transcipts from *SMN2*, lack exon 7, leading to production of only minimal amounts of functional SMN. SMA patients have mutations or deletions in *SMN1* and rely on *SMN2* for SMN production, resulting in severe SMN deficiency.



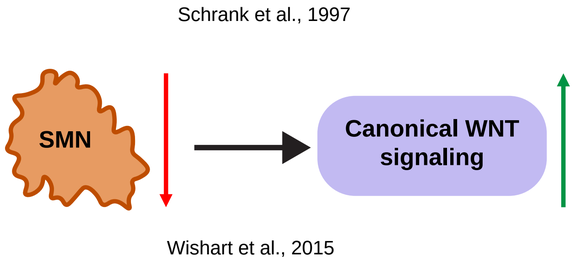
SMN is critical for **RNA splicing** and is **highly expressed** during neural **development**. Complete SMN knock-out in mouse embryos results in death at late morula stage. Severe SMA mice models exhibit reduced brain size by postnatal day 6. Further research revealed increased WNT signaling activity in SMA tissues, raising questions about its impact on normal embryonic development. We therefore hypothesized that **SMN deficiency alters early developmental processes, which could drive MN degeneration in SMA.**



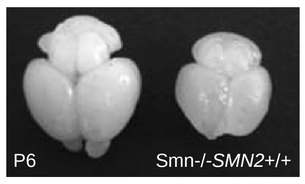
Schrank et al., 1997



Burlet et al., 1998
Gabanella et al., 2005
Ramos et al., 2019



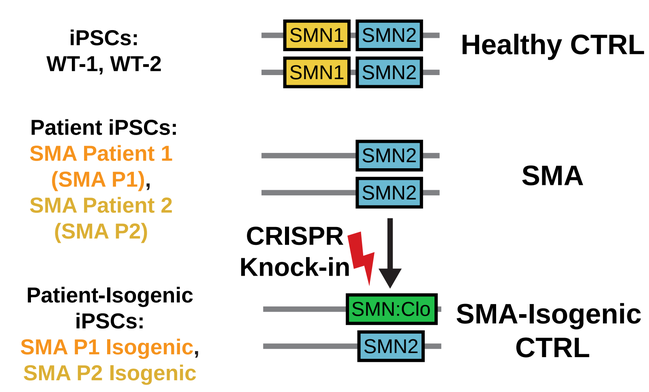
Wishart et al., 2015



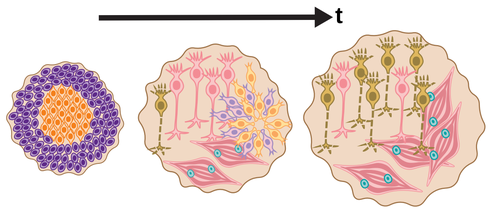
Wishart et al., 2010

Methods

Cohort of hiPSCs



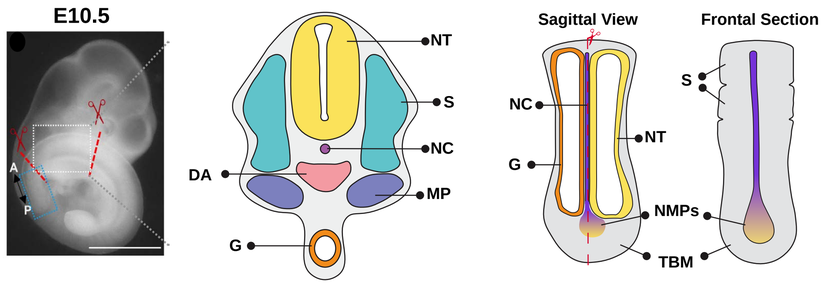
Ventral Neuromuscular Organoids (NMOs)

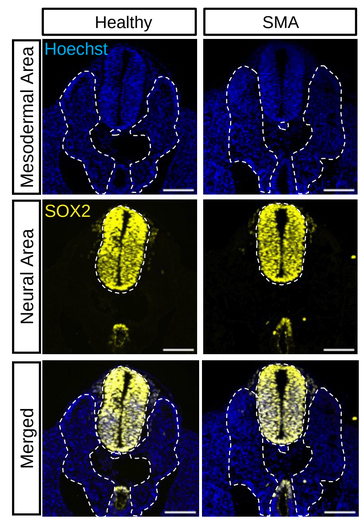


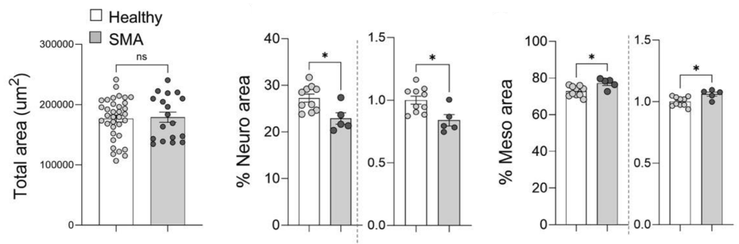
SMA Mouse Model

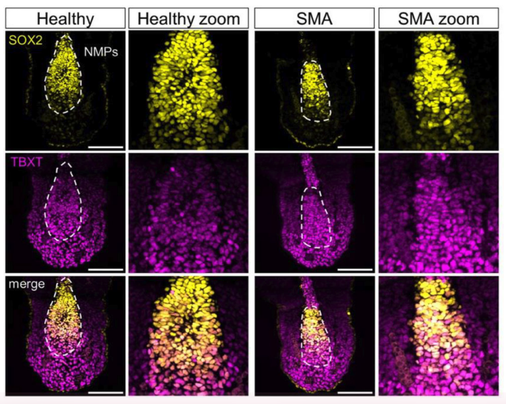
Smn-/- *SMN2*+, *SMNdelta7*+
Hb9:GFP

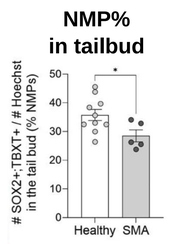
Early Neuromesodermal Fate Commitment Defects in SMA Mouse Embryos





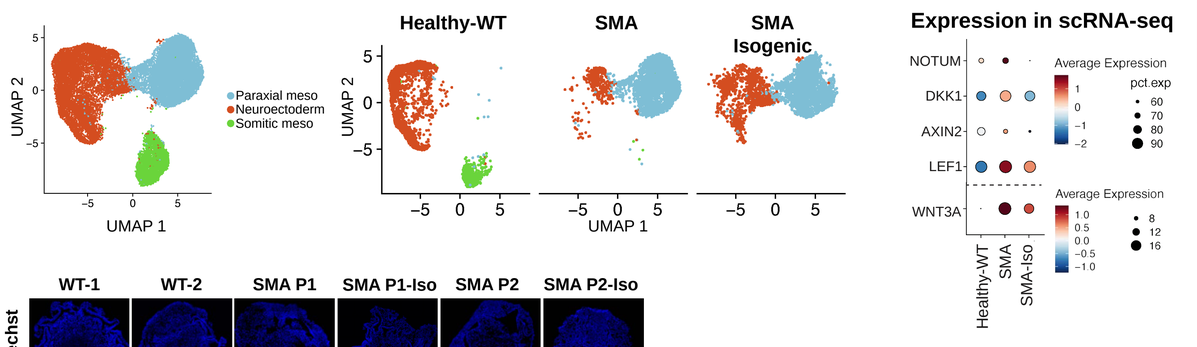


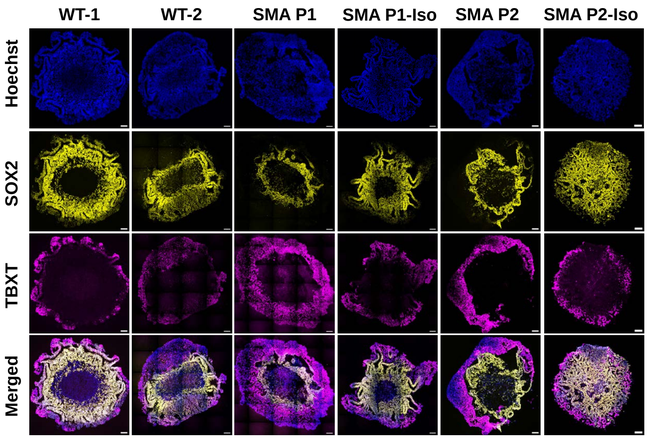


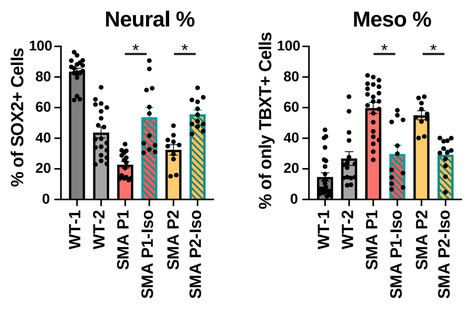


- Lumbar segments of E10.5 SMA embryos revealed an approximately 18% reduction in neural tube size, while mesodermal tissues were enlarged.
- NMPs were less prominent in the tailbuds of SMA E10.5 embryos, suggesting an earlier exhaustion.

scRNA-seq Reveals a Mesodermal Bias in Early SMA NMOs







REFERENCES

1. Grass, T., **Dokuzluoglu, Z.**, Buchner, F., Rosignol, I., Thomas, J., Caldarelli, A., Dalinskaya, A., Becker, J., Rost, F., Marass, M., Wirth, B., Beyer, M., Bonaguro, L., & Rodriguez-Muela, N. (2024). Isogenic patient-derived organoids reveal early neurodevelopmental defects in spinal muscular atrophy initiation.
2. Grass, T., **Dokuzluoglu, Z.**, & Rodríguez-Muela, N. (2024). Neuromuscular Organoids to Study Spinal Cord Development and Disease. Methods in Molecular Biology

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Questions/comments are appreciated!