Systemic pathology in spinal muscular atrophy (SMA)

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SMA as a multi-system disorder

Hamilton & Gillingwater 2013. Trends Mol Med
SMA as a multi-system disorder

Subcutaneous injection increased median survival from 17 to 100+ days compared to ICV injection
NMJ pathology in SMA mice

NMJ pathology in SMA patients

Pre-natal NMJ pathology in SMA patients

Could muscle defects cause NMJ pathology in SMA?

McCann et al 2007. J Neurosci
Could glial defects cause NMJ pathology in SMA?

WT mouse

Prx-/- mouse

Prx-/- mouse

Prx-/- mouse

Court et al 2008. Glia
Schwann cell pathology in SMA mice

(a) Control

SMA

(c) Non-myelinated axons >1μm diameter (% of total)

Control

SMA

(d) G Ratio

Control

SMA

Schwann cell pathology in SMA patients

• MN loss correlates with a reduction in the number and diameter of large myelinated motor axons

• Increase in the proportion of small, immature, unmyelinated motor axons suggests an impairment of axon development in Type I SMA patients
Reversible/SMN-dependent Schwann cell pathology

Restoring SMN in Schwann cells in vivo

Vascular defects in skeletal muscle: SMA mice

A
Control

B
SMA

C

D

E

Capillary area / muscle (%)

Capillaries / muscle fibre

Intramuscular arterioles / section

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Control
SMA

Vascular defects in skeletal muscle: SMA patients
Vascular defects in spinal cord: SMA mice

A
Control

B
SMA

C
Relative Capillary Density/
Unit Area of Spinal Cord

P0
P5
P11

ns
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Vascular defects lead to hypoxia in spinal cord
Model of systemic susceptibility to low SMN levels

Relative viability

Largely unaffected

Beginning to deteriorate

Severely affected

SMA Type

0  I  II  III  IV

Other Cells & Tissues

Sensory Neurons, Heart, Bone, Hippocampus

Motor Neurons

% normal SMN levels

~10-20%  ~35-45%

Sleigh et al 2011. Disease Models & Mechanisms
Acknowledgements