Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis

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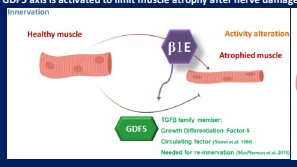
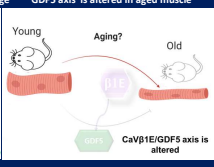
Introduction

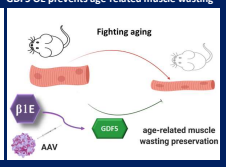
GDF5 axis is activated to limit muscle atrophy after nerve damage

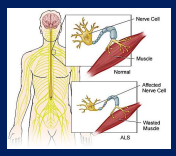


GDF5 axis is altered in aged muscle



GDF5 OE prevents age-related muscle wasting





ALS

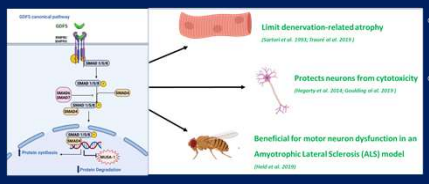
- The most common adult-onset motor neuron disorder (1-4 per 100.000 live birth per year)
- 90% sporadic forms, 10% familial forms
- Very rapid progression: death often occurs within 3 - 5 years of diagnosis
- Multifactorial pathophysiological mechanisms
- No cure: More than 50 negative randomized controlled clinical trials in the past 50 years

Muscle denervation is a common hallmark of several neuromuscular diseases and accounts for skeletal muscle atrophy and dysfunction associated to their pathophysiology. In non-pathologic muscle, the induction of GDF5/SMAD1/5 pathway is essential for avoiding excessive atrophy but also for promoting re-innervation after nerve damage.

Recently, we demonstrated that alterations of GDF5 pathway can be implicated in human and mouse age-related muscle wasting and that its overexpression prevents muscle mass loss and force decline during ageing in mice.

SMAD1/5 pathway activation has been described as beneficial for motor neuron dysfunction in an Amyotrophic Lateral Sclerosis (ALS) model. We thus hypothesize that GDF5 implementation could have a positive impact on pathophysiology of the disease. We propose a strategy potentially applicable to different ALS forms and/or to optimize gene therapy-based approaches.

Therapeutic potential of GDF5 in ALS



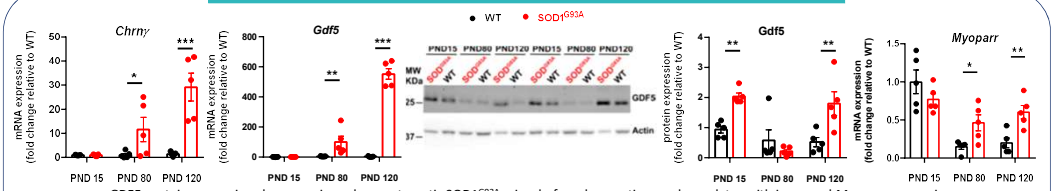
ALS-linked mutations: SOD1

- 20% of the familial cases are caused by toxic gain of function mutations in the Cu/Zn superoxide dismutase-1 gene (SOD1)
- Modeling by mutant hSOD1 overexpression

SOD1-G93A mouse

- ✓ Abbreviated lifespan (128.9+/-9.1 days)
- ✓ Paralysis
- ✓ Rapid disease progression
- ✓ Motor neuron degeneration
- ✓ Astrogliosis
- ✓ Severe muscle weakness

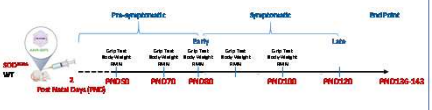
Endogenous GDF5 expression during ALS progression in SOD^{G93A} mice



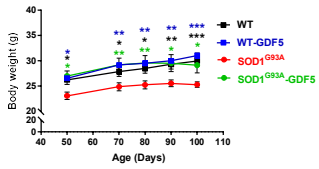
GDF5 protein expression decreases in early symptomatic SOD1^{G93A} mice, before denervation, and correlates with increased Myoparr expression

*Data are means ± SEM (n=5 mice/group); *P < 0.05, **P< 0.01 and ***P < 0.001. Two-way ANOVA (Fisher's)*

GDF5 Overexpression (OE) in SOD^{G93A} mice



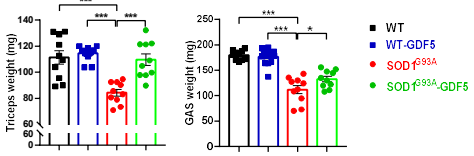
GDF5 overexpression and ALS progression in SOD^{G93A} mice

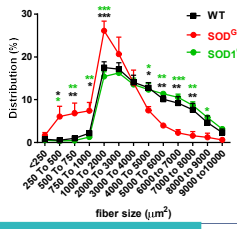


GDF5 OE induces increase of body weight of SOD1^{G93A} mice (PND 100)

*Data are means ± SEM (n=5 mice/group); *P < 0.05, P< 0.005 and ***P < 0.001. Two-way and one-way ANOVA (Dunnett's)*

GDF5 overexpression and muscle mass

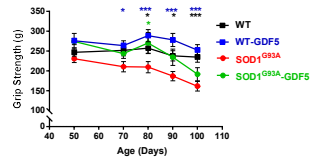




GDF5 OE induces increase in muscle mass and fiber size in SOD1^{G93A} mice (PND 100)

*Data are means ± SEM (n=5 mice/group); *P < 0.05, P< 0.005 and ***P < 0.001. One-way (Dunnett's) and two-way and ANOVA*

Force generation of GDF5 overexpressing SOD^{G93A} mice

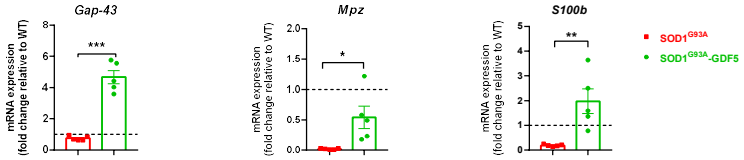


GDF5 OE delays force decline of SOD1^{G93A} mice

*Data are means ± SEM (n=5 mice/group); *P < 0.05, and ***P < 0.001. one-way ANOVA (Dunnett's)*

Nerve regeneration markers

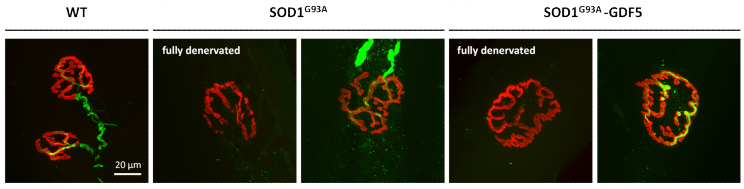
Growth-associated protein 43 (GAP43), associated with regenerating axons and Schwann cells, Myelin Protein Zero (MPZ) and S100b increase during nerve regeneration

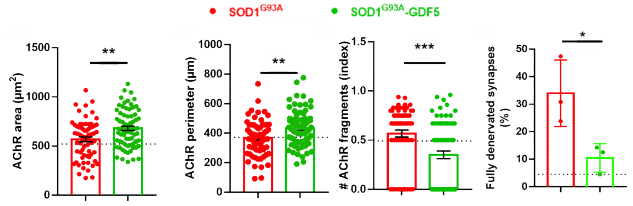


GDF5 OE induces increase of transcripts associated to nerve regeneration suggesting a protective role of this factor against motoneuron degeneration observed in ALS.

*Data are means ± SEM (n=5 mice/group); *P < 0.05, **P< 0.01 and ***P < 0.001. Independent samples t-test (two tailed). Dotted black lines indicate the average of expression in age-matched WT mice.*

Neuromuscular junction morphology and innervation





Synapses are more stable in GDF5 OE muscles, with increased endplates area and perimeters and decreased AChR fragmentation index and percentage of fully denervated synapses

Acetylcholine Receptor (α-bungarotoxin)
Nerves terminals (Synaptophysin) .

*Data are means ± SEM (n= 66/75 counted endplates=3 mice/group); *P < 0.05, **P< 0.01 and ***P < 0.001. Independent samples t-test (two tailed). Dotted black lines indicate the average of expression in age-matched WT mice*

Conclusions

Benefits of GDF5 overexpression in ALS:

- ✓ Maintains muscle mass and fibers size and delays grip strength decline
- ✓ Shows a positive impact on nerve regeneration markers
- ✓ Exerts a protective effect against muscle denervation

Perspectives

Establishment of GDF5 therapeutic potential in ALS

- ✓ Effects of GDF5 on neuro-inflammation, motor neuron viability and survival
- ✓ Evaluation of tissue-specific GDF5 expression on ALS pathophysiology
- ✓ Therapeutic test of GDF5 in adult ALS mice and in combination with a gene therapy

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