Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis

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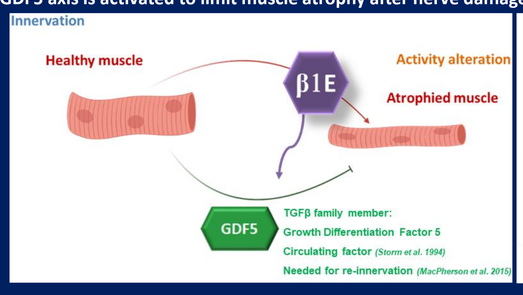
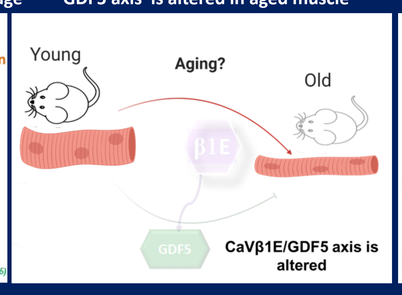
Introduction

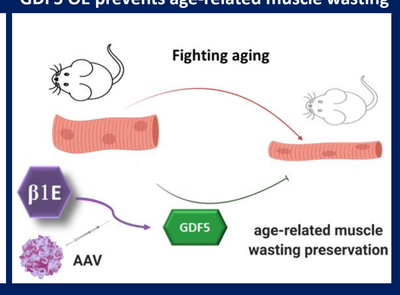
GDF5 axis is activated to limit muscle atrophy after nerve damage



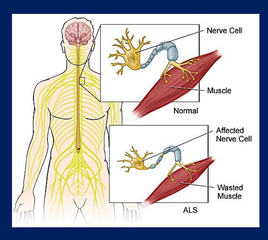
GDF5 axis is altered in aged muscle



GDF5 OE prevents age-related muscle wasting



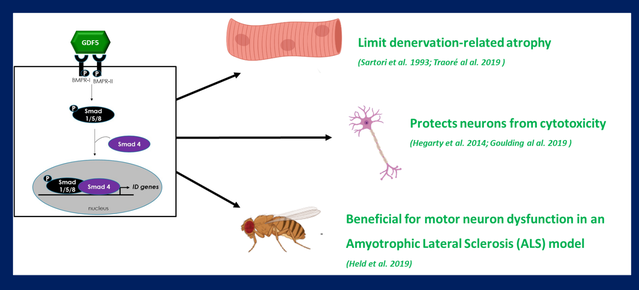
Muscle denervation is a common hallmark of several neuromuscular diseases and accounts for skeletal muscle atrophy and dysfunction associated to their pathophysiology. In non-pathologic muscle, the induction of GDF5/SMAD1/5 pathway is essential for avoiding excessive atrophy but also for promoting re-innervation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



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

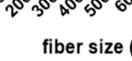
Therapeutic potential of GDF5 in ALS



ALS-linked mutations: SOD1

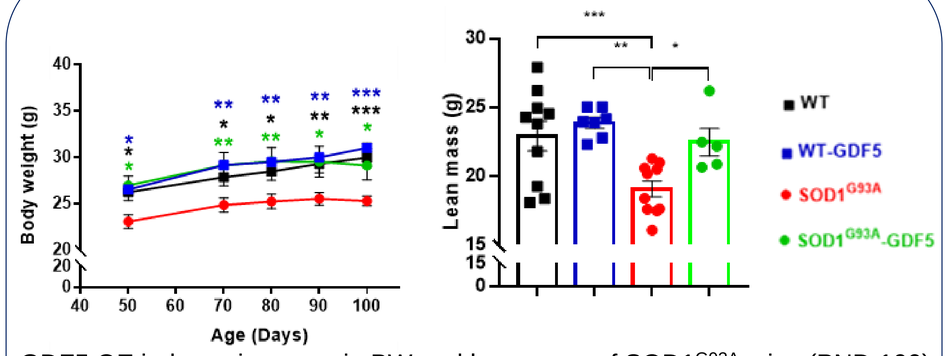
- 20% of the familial cases are caused by toxic gain of function mutations in the Cu/Zn superoxide dismutase-1 gene (SOD1)
- Modeling by mutant hSOD1 overexpression

SOD1-G93A mouse



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

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



GDF5 OE induces increase in BW and lean mass of SOD1^{G93A} mice (PND 100)

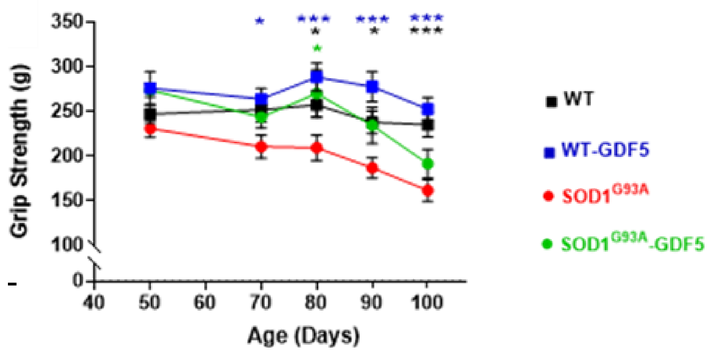
*Data are means ± SEM (n=5 mice/group); *P < 0.05, P< 0.005 and ***P < 0.001. Two-way and one-way ANOVA (Dunnett's)*

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

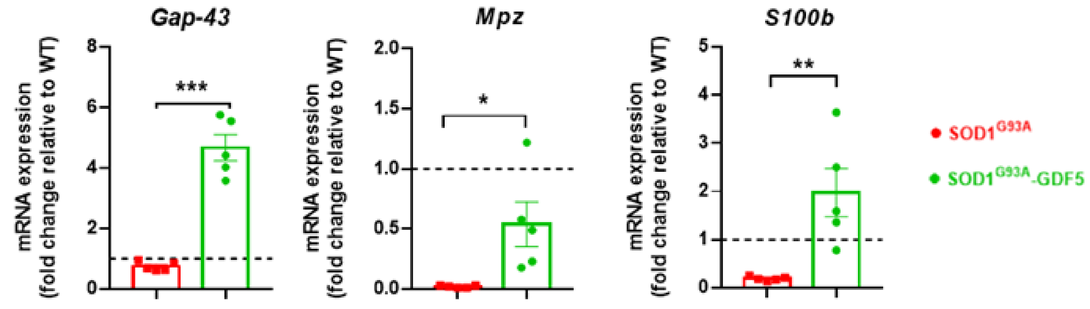


GDF5 OE delays force decline of SOD1^{G93A} mice

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

Nerve regeneration markers

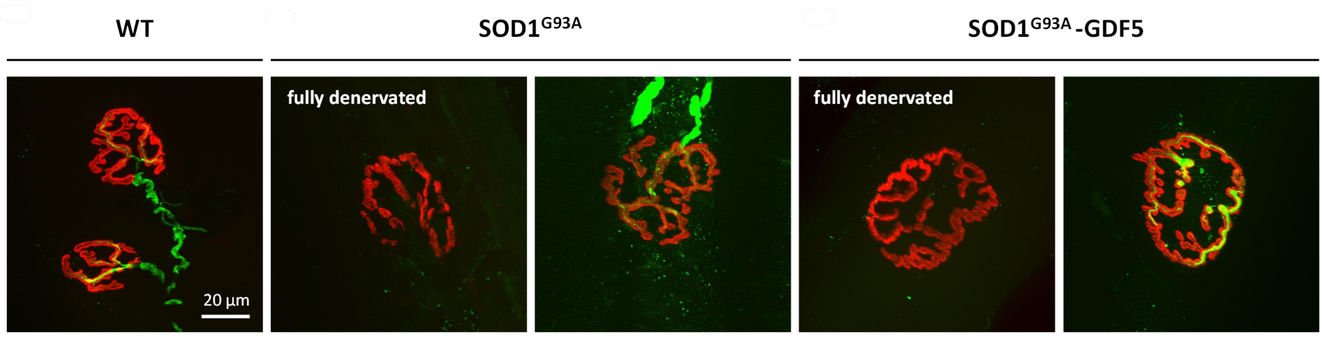
Growth-associated protein 43 (GAP43): associated with regenerating axons and Schwann cells, Myelin Protein Zero (MPZ) and S100b increase during nerve regeneration



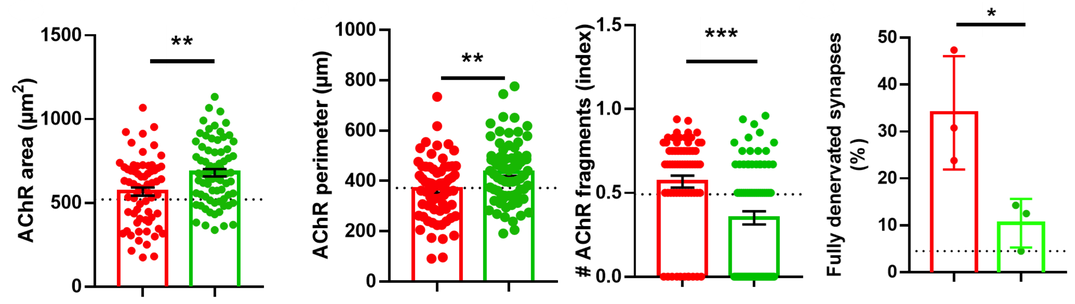
GDF5 OE induces increase of transcripts associated to nerve regeneration suggesting a protective role of this factor against MN degeneration observed in ALS.

*Data are means ± SEM (n=5 mice/group); *P < 0.05, P< 0.005 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



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



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

*Data are means ± SEM (n= 66/75 counted endplatesn=3 mice/group); *P < 0.05, P< 0.005 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 GFD5 in adult ALS mice and in combination with a gene therapy

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