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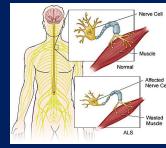
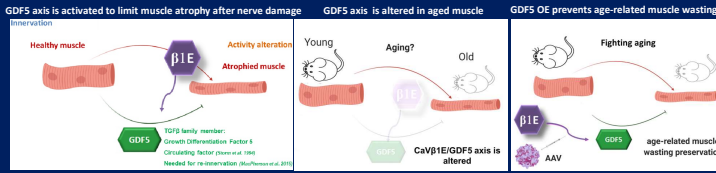
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Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis

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Introduction

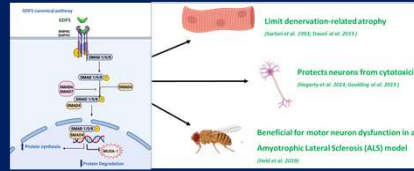


ALS

- 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.

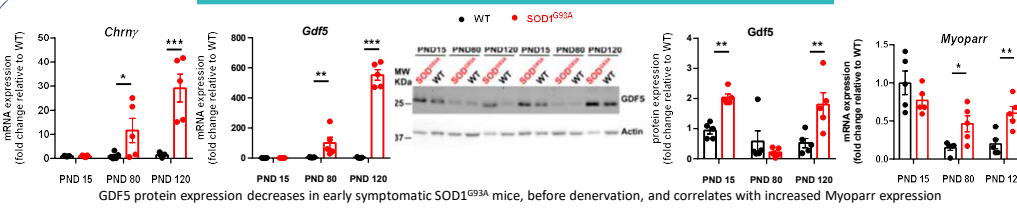
Therapeutic potential of GDF5 in ALS



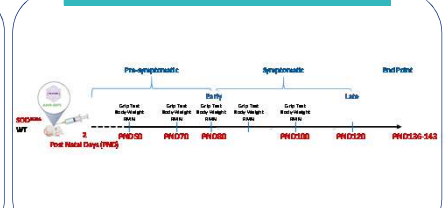
ALS-linked mutations: SOD1

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

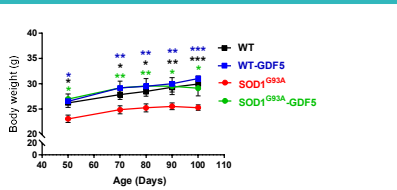
Endogenous GDF5 expression during ALS progression in SOD1^{G93A} mice



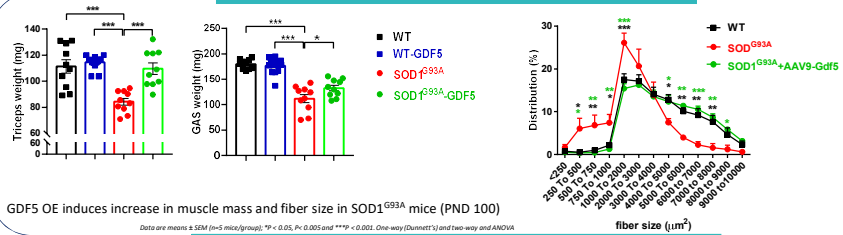
GDF5 Overexpression (OE) in SOD1^{G93A} mice



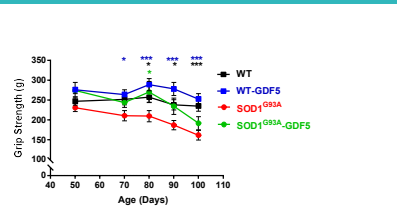
GDF5 overexpression and ALS progression in SOD1^{G93A} mice



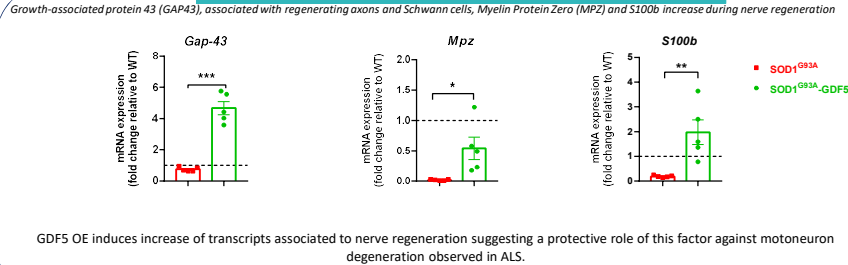
GDF5 overexpression and muscle mass



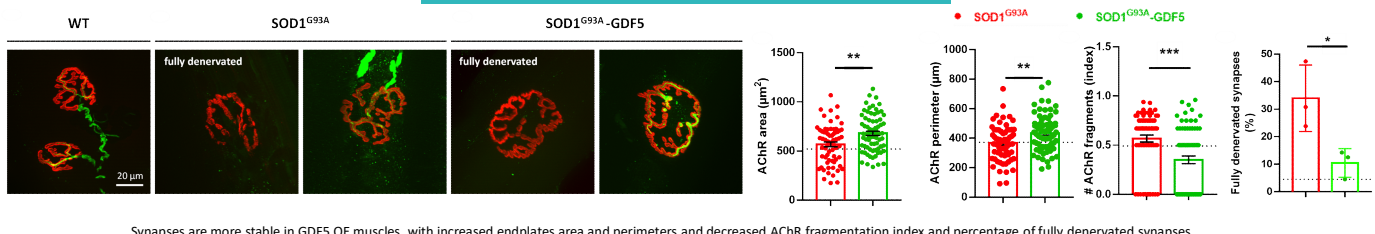
Force generation of GDF5 overexpressing SOD1^{G93A} mice



Nerve regeneration markers



Neuromuscular junction morphology and innervation



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