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GDF5 therapeutic potential for DMD

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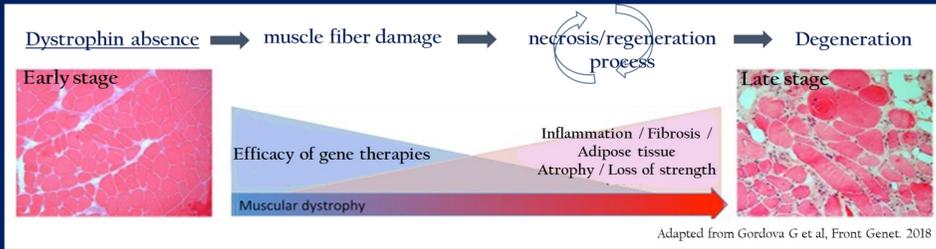
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GDF5 therapeutic potential for DMD

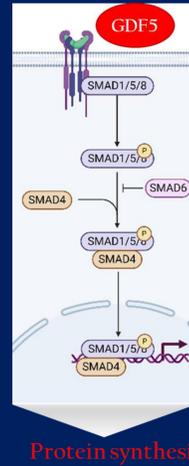
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Introduction



Duchenne muscular dystrophy (DMD) is a devastating neuromuscular disease caused by the lack of the dystrophin protein. Among therapeutic strategies, clinical trials with AAV administration of microDystrophin (AAV- μ Dyst) are underway and the first data indicate the potential of gene therapy as treatment to respond to unmet need for DMD. However, these approaches target the degenerating musculature and a major limitation is the loss of therapeutic benefits during necrosis/regeneration process. Maintaining muscle mass for as long as possible in order to optimize gene therapy is of major interest for the long-term success of these strategies.

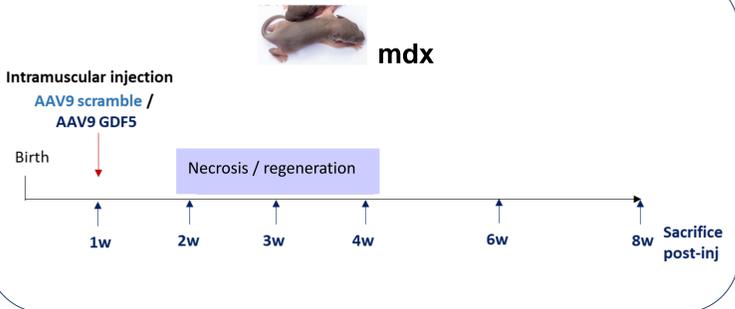


In terms of muscle mass homeostasis, an emerging relevance is observed for components of Bone Morphogenetic Protein (BMP) family such as BMP14 also called Growth Differentiation Factor 5 (GDF5). GDF5 signaling includes the phosphorylation of intracellular SMAD1/5/8 complex, which translocates to the nuclei and controls gene transcription.

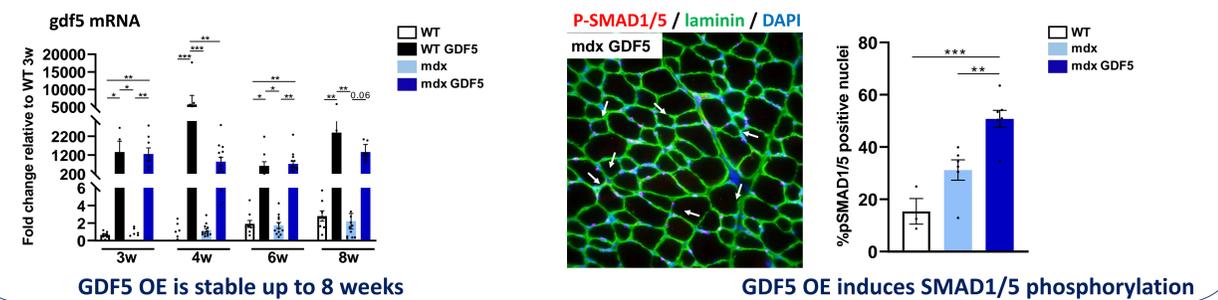
Our previous work showed that GDF5 prevents both muscle mass loss and force decline during ageing (Traoré et al, 2019). In addition, its signaling has been described as a positive modulator of muscle mass homeostasis (Winbanks et al, 2013) and a potential regulator of muscle repair (Borok et al, 2020).

Here, we investigated the impact of GDF5 overexpression (OE) on the progression of DMD pathophysiological features in mdx mice (a DMD mouse model).

Protocol



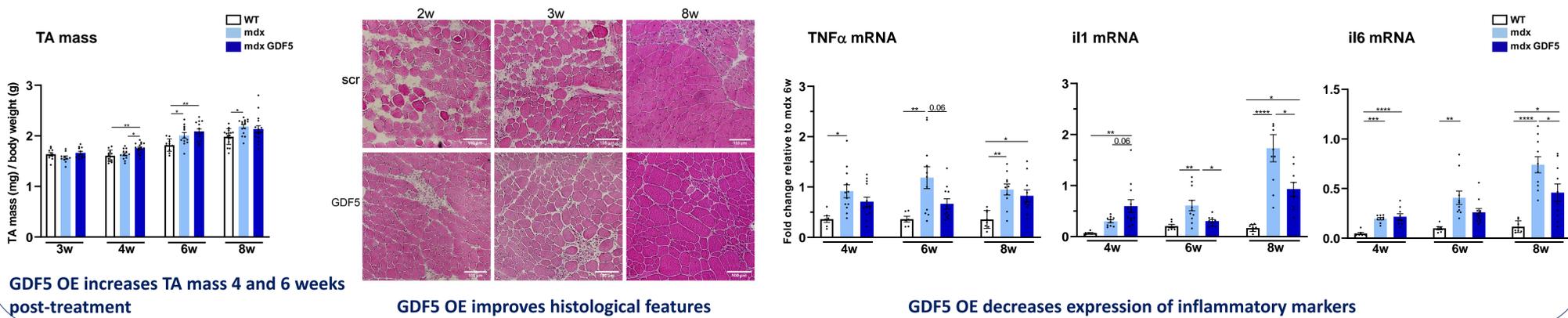
GDF5 overexpression and SMAD1/5 pathway activation



GDF5 OE is stable up to 8 weeks

GDF5 OE induces SMAD1/5 phosphorylation

Effects of GDF5 overexpression on DMD muscle pathophysiology

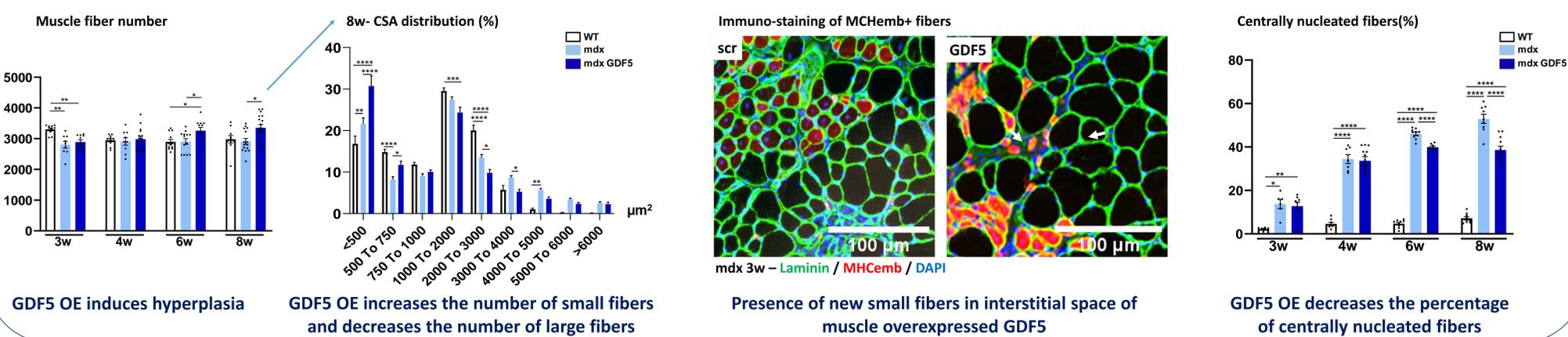


GDF5 OE increases TA mass 4 and 6 weeks post-treatment

GDF5 OE improves histological features

GDF5 OE decreases expression of inflammatory markers

GDF5 overexpression and the differentiation / regeneration process



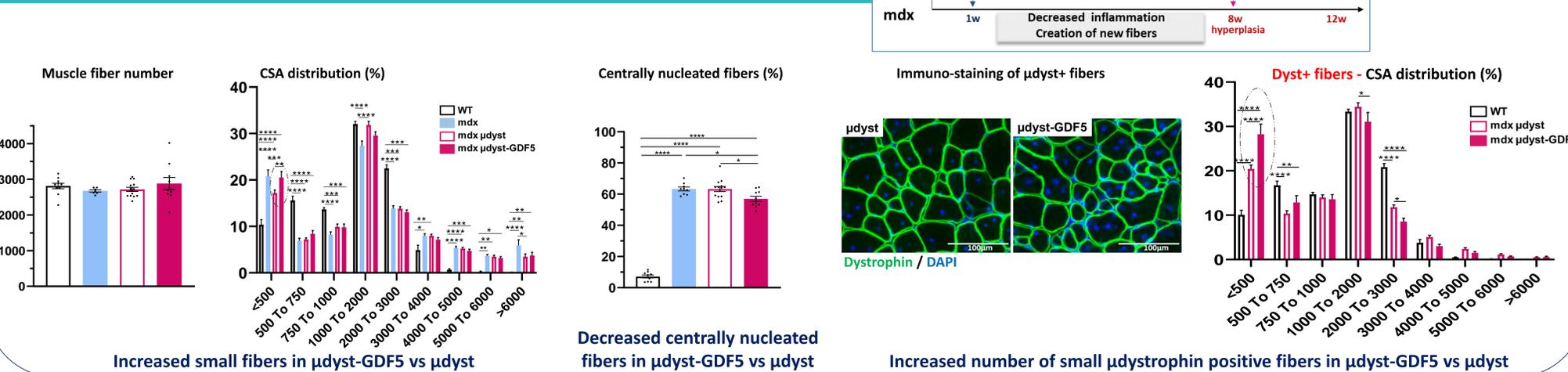
GDF5 OE induces hyperplasia

GDF5 OE increases the number of small fibers and decreases the number of large fibers

Presence of new small fibers in interstitial space of muscle overexpressed GDF5

GDF5 OE decreases the percentage of centrally nucleated fibers

A combined treatment to optimize gene therapy : AAV-GDF5 and AAV- μ dystrophin



Increased small fibers in μ dyst-GDF5 vs μ dyst

Decreased centrally nucleated fibers in μ dyst-GDF5 vs μ dyst

Increased number of small μ dystrophin positive fibers in μ dyst-GDF5 vs μ dyst

Conclusions

- GDF5 overexpression in muscle of DMD mice model (mdx)
- Improves histological features and slows down the necrosis/regeneration process
- Induces hyperplasia with new small fibers in muscle interstitial space
- Increases number of small μ dystrophin positive fibers in μ dyst+GDF5 vs μ dyst treatment alone

Perspectives

- Identify of GDF5 target cells underpinning the observed hyperplasia
- Investigate benefits of a combined treatment with sGDF5 protein and AAV- μ Dyst