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Galectin-1: A Potential Protein Therapy for Limb-Girdle Muscular Dystrophy 2B

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Introduction

- Limb-Girdle Muscular Dystrophy 2B (LGMD2B) belongs to a group of diseases called dystrophinopathies, caused by mutations in the DYSF gene.
- Dysferlin is an important muscle membrane protein involved in repair and regeneration after injury.
- LGMD2B causes muscle wasting, fat infiltration, and loss of ambulation in patients.
- Currently there is no cure and few treatment options.
- Galectin-1 is a small protein that interacts with glycosylated proteins. It shows efficacy in treating mouse models of Duchenne Muscular Dystrophy.
- Here we explore the ability of recombinant human Galectin-1 (rHsGal-1) to ameliorate disease pathologies and mechanisms of LGMD2B.

Hypothesis

Possible roles for Galectin-1 Protein Therapy in LGMD2B

- Absence of functional Dysferlin
- Membrane Damage
  - Unrepaired Membrane Damage
  - Reduced Myogenesis
  - Muscle Fibre Death
  - Muscles Degeneration

Hypothesis: Recombinant human galectin-1 (rHsGal-1) protein treatment will improve membrane repair of LGMD2B models thus increasing myogenesis, stabilizing muscle integrity, and decreasing disease manifestation.

Results

rHsGal-1 Synthesis and Purification

The DNA encoding for LGALS1 was cloned into the pET29B (+) vector and over expressed in BL21 (DE3) competent E. coli cells. The purity of galectin-1 was analyzed using western blot with anti-Galectin-1 and anti-His.

Increased Myogenesis

0.11µM rHsGal-1 is the optimal dose for increasing myogenic expression. Non-treated A/J - cells (NT) and A/J - cells treated with rHsGal-1, with doses ranging from 0.014µM to 0.22µM, were analyzed using anti-muscle antibody to determine the optimal dose of rHsGal-1 needed to increase myogenesis. We saw a 1.8 fold increase in myogenin, a transcription factor associated with late stages of myogenesis, expression at a dose of 0.11µM rHsGal-1 compared to NT.

Increased Membrane Repair

A/J - myotubes and myoblasts treated with rHsGal-1 have increased membrane repair capacity. Treated and non-treated A/J - myotubes were injured by UV laser in the presence of FITC-488 dye and the membrane repair capacity was quantified by measuring the change in fluorescent intensity with doses ranging from 0.054µM to 0.11µM rHsGal-1. An improvement after 10min of treatment indicates that the repair mechanism is independent of myogenesis. Likewise, we saw that rHsGal-1 closed faster and more completely than NT myoblasts. For particular interest, it qualitatively appears that cells treated with rHsGal-1 form myotubes in the wound area during the 4hrs after the injuries were removed, while non-treated cells do not. This helps to explain previous results that indicate rHsGal-1 can increase fusion and maturation of myotubes to muscle. Likewise, it shows that rHsGal-1 can increase migratory factors, which are linked to better in vivo muscle repair.

Conclusions

- rHsGal-1 increases myogenic regulatory factors and myotube formation.
- A/J - myotubes treated with rHsGal-1 have increased membrane repair capacity.
- The CRD of galectin-1 is responsible for increased membrane repair and dystrophin deficient myotubes.
- Wound healing in accelerated with rHsGal-1 treatment.
- Galectin-1 transcript levels are up regulated with rHsGal-1 treatment.
- NPe-R pathway is downregulated with rHsGal-1 treatment in a time sensitive manner.

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