Animal models for muscular dystrophy; mechanism of disease and potential therapy

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ABSTRACT

The aim of this study was to test the therapeutic effects of ADAM12, a metalloprotease and disintegrin protein, in two mouse models for muscular dystrophy, and to try to understand better the mechanisms of muscular dystrophy through the analysis of experimental or spontaneous animal models for muscular dystrophy, including mice, dogs, and cats. This study was conducted in Dr Ulla Wewer's laboratory at the Institute of Molecular Pathology at the University of Copenhagen, Denmark, and in Dr Eva Engvall's laboratory at the Burnham Institute in La Jolla, USA.

ADAM12 is a protein, which is associated with muscle development and regeneration. Overexpression of a membrane anchored human ADAM12 in dystrophin deficient mdx muscle resulted in stabilized muscle cell membrane and reduced muscle necrosis. In this study, we found that overexpression of ADAM12 up-regulated and redistributed several cell adhesion protein complexes – integrin α7B, utrophin, and dystrophin-associated-glycoproteins. This up-regulation apparently stabilized the cell membrane in dystrophin deficient mdx muscle, and thereby prevented necrosis and consequent destructive pathway to muscular dystrophy. Further work is required to determine how ADAM12 up-regulated these protein complexes.

We also studied to what extent overexpression of ADAM12 may benefit laminin α2-deficient dyW mouse. The dyW mouse has insufficient regeneration and has a much more severe form of muscular dystrophy than the mdx mouse. We found slightly increased regeneration upon ADAM12 overexpression as evidenced by increased number of fibers with positive staining for embryonic myosin heavy chain in transgenic dyW mouse muscle. However, body weight and muscle histology showed little improvement. We did not find difference in levels of protein expression of integrin, utrophin, and dystrophin-associate proteins in dyW muscle with or without ADAM12 transgene. The conclusion is that dyW mice did not benefit enough from ADAM12 overexpression in muscle in contrast to the beneficial effect on mdx mice. This study emphasized the importance of using multiple animal models to test any new therapy that does not target a specific gene defect.

We have analyzed a series of laminin α2 mutant mice and found that the level of laminin α2 protein in the muscle is indirectly correlated with the severity of muscular dystrophic. The amount of protein is more important than minor structural defects in the laminin α2 molecule, such as lack of domain VI. We have also performed immunodiagnosis in 60 cases of dogs and cats with muscular dystrophy. We found that dystrophin deficiency is the most common form of MD in dogs and cats as it is in humans. We also found dogs and cats with laminin α2 and sarcoglycan deficiency. The identification of dogs and cats with defined forms of muscular dystrophy may allow the establishment of breeding colonies that could provide alternative models for future muscular dystrophy research, particularly for the testing of potential new therapies.