

# LGMD2D myotubes

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LGMD2D (LGMD-R3 according to the new nomenclature) is a rare autosomal recessive disease affecting striated muscle. It belongs to the group of limb girdle muscular dystrophies because of the involvement of the proximal musculature of the shoulders and pelvic girdle. LGMD2D is caused by mutations in the *SGCA* gene coding for  $\alpha$ -sarcoglycan (SG).

rare disease    muscular dystrophy    folding defective protein    pathogenic mechanism  
endoplasmic reticulum associated degradation    small molecules    pharmacological  
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## 1. Introduction

The Limb girdle muscular dystrophy type 2D (LGMD2D) is a rare autosomal recessive disease affecting mainly the upper and lower hind limb musculature, with no cure presently available. The disease, also known as  $\hat{\Gamma}$ -sarcoglycanopathy is due to mutations of the *SGCA* gene coding for the membrane protein  $\hat{\Gamma}$ -sarcoglycan (SG). Together with  $\hat{\Gamma}^2$ -,  $\hat{\Gamma}^3$ - and  $\hat{\Gamma}'$ -SG,  $\hat{\Gamma}$ -SG forms the SG-complex that concurs with other dystrophin-associated proteins (DAPs) in the stabilization of the sarcolemma during the contraction of the striated muscle. The absence or strong reduction of the SG-complex is the main feature of LGMD2D that results in increased sarcolemma fragility and consequent progressive muscle degeneration. Most of the *SGCA* defects are missense mutations originating a folding defective, although potentially functional protein recognized by the endoplasmic reticulum (ER) quality control system and eliminated through the ER associated degradation (ERAD). To recover the mutants and escape SG-complex disruption, an approach was based on the use of protein folding correctors belonging to the CFTR (cystic fibrosis transmembrane regulator) modulators family, first developed to treat cystic fibrosis. Several of such compounds rescued different  $\hat{\Gamma}$ -SG mutants expressed in cell models, and importantly their administration in primary myotubes of a LGMD2D patient improved the mutant folding, and the assembly and traffic of the SG-complex. The rescued complex was stable and functional and improved the sarcolemma behavior, even though containing a mutated subunit. Understanding the mechanism of action of CFTR correctors in sarcoglycanopathy will be mandatory; however, these findings suggest that these small molecules have the potential to progress as therapeutics for LGMD2D caused by missense mutations.

## 2. Description

LGMD2D (LGMD-R3 according to the new nomenclature <sup>[1]</sup>) is a rare autosomal recessive disease affecting striated muscle. It belongs to the group of limb girdle muscular dystrophies because of the involvement of the proximal musculature of the shoulders and pelvic girdle <sup>[2]</sup>. LGMD2D is caused by mutations in the *SGCA* gene coding for  $\hat{\Gamma}$ -sarcoglycan (SG) <sup>[3]</sup><sup>[4]</sup><sup>[5]</sup>. This protein, together with  $\hat{\Gamma}^2$ -,  $\hat{\Gamma}^3$ - and  $\hat{\Gamma}'$ -SG, forms the SG complex, a key component of the dystrophin associated protein complex, significantly helping to preserve sarcolemma from contraction-induced stress. Moreover, a number of direct or indirect regulative roles have been attributed to the SG-complex <sup>[6]</sup><sup>[7]</sup>. LGMD2D, although heterogeneous, is often characterized by early onset and rapid progression, with people affected becoming wheelchair-bound during the adolescence <sup>[8]</sup>.

Presently, no effective therapy is available for LGMD2D as well as for the other three forms of sarcoglycanopathy (LGMD2E, 2C and 2F, due to mutations in SGCB, SGCG and SGCD genes, respectively [9]). Most of the gene defects responsible for the onset of sarcoglycanopathy are missense mutations [10][11][12][13]. In the last few years, the pathogenic mechanism of the forms of sarcoglycanopathy due to this type of genetic defect has been disclosed. It has been observed that many sarcoglycans with an amino acid substitution are unable to properly fold, are recognized by the quality control system of the cells and delivered to a premature degradation [14][15][16][17]. Consequently, the correct assembly, traffic and localization of the SG-complex is impaired, leading to a global reduction in the structural stability of the sarcolemma. An interesting point is the possibility to rescue the defective sarcoglycan as well as the entire SG-complex, by preventing the degradation of the mutant, acting either at the initial [15][16], intermediate [17] or final step [14] of the pathway. On these premises, a novel strategy of therapeutic intervention was elaborated [18] also taking advantage of the tremendous work done on another genetic disease, cystic fibrosis that shares with sarcoglycanopathy a similar pathogenic mechanism [19]. This approach is based on the use of small molecules known as cystic fibrosis transmembrane regulator (CFTR) correctors, which were originally selected and developed to improve folding and traffic of defective CFTR protein (type II mutants) [20][21][22]. In cystic fibrosis, some of these compounds act as pharmacological chaperones, directly binding to the mutated CFTR [23], while others play an indirect action, as modulators of the cell proteostasis [24]. Regardless of the mechanism, CFTR correctors have been proven effective not only on CFTR mutants but also on structurally correlated [25] as well as structurally uncorrelated defective proteins [26][27] such as  $\beta$ -SG [18,28]. Indeed, the outcome of the administration of CFTR correctors to LGMD2D myotubes is the enhanced assembly of the SG-complex that re-gains the ability to traffic toward the sarcolemma. Once at the final location the SG-complex containing the corrected subunit seems stable and functional. The combined administration of two CFTR correctors may result in additive/synergistic effects [18][28]. These data support the view that several CFTR corrector could be effective in conditions different from cystic fibrosis, such as LGMD2D, suggesting new therapeutic opportunities for orphan diseases currently incurable.

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