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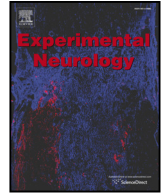

Review Article

Dysferlin function in skeletal muscle: Possible pathological mechanisms and therapeutical targets in dysferlinopathies

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ABSTRACT

Mutations in the dysferlin gene are linked to a group of muscular dystrophies known as dysferlinopathies. These myopathies are characterized by progressive atrophy. Studies in muscle tissue from dysferlinopathy patients or dysferlin-deficient mice point out its importance in membrane repair. However, expression of dysferlin homologous proteins that restore sarcolemma repair function in dysferlinopathy animal models fail to arrest muscle wasting, therefore suggesting that dysferlin plays other critical roles in muscle function. In the present review, we discuss dysferlin functions in the skeletal muscle, as well as pathological mechanisms related to dysferlin mutations. Particular focus is presented related the effect of dysferlin on cell membrane related function, which affect its repair, vesicle trafficking, as well as Ca^{2+} homeostasis. Such mechanisms could provide accessible targets for pharmacological therapies.

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1. Introduction

The hereditary myopathies comprise a large family of degenerative muscular disorders genetically determined by over 350 different mutations in distinct genes, for which novel causing mutations and genes are identified each year (Kaplan and Hamroun, 2014). The pathological

Abbreviations: LGMD, limb girdle muscular dystrophy; CK, creatine kinase levels; MG53, mitsugumin 53; Cx, connexins; TRPV2, transient receptor potential vanilloid type 2; STB, syncytiotrophoblasts.

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mechanisms underlying these ailments are largely unknown, and therapy mostly lies within the realm of tertiary care. Among these, muscular dystrophies represent a sizable amount of such disorders, with a worldwide distribution and an estimated incidence of 1/2000 live births. Although the genetic background is clear for most muscle dystrophies, their pathophysiology remains elusive. Indeed, mutations that render truncated or dysfunctional proteins that are critical for normal muscle integrity and function is a common feature of these disorders, but the underlying mechanisms by which such mutations result in the compromise of the skeletal muscle remain unclear. Moreover, in many cases the lack of knowledge of the function of the protein in question is the key issue. Among the causes of such myopathies are those linked to mutations in the dysferlin gene (DYSF), a large-sized gene spanning over 150 kb of genomic DNA that is located on chromosome 2p13 (Bashir et al., 1998; Liu et al., 1998; Aoki et al., 2001) and that produces a 237 kDa single-pass transmembrane protein (Anderson et al., 1999; Matsuda et al., 1999).

Reduction or absence of dysferlin, resulting from autosomal recessive mutations in the gene that encodes for DYSF [MIM# 603009, GenBank NM_003494.2] comprises a number of different muscular dystrophy phenotypes known as dysferlinopathies. The term dysferlinopathy was introduced after setting forth that Miyoshi's myopathy (MM) and limb girdle muscular dystrophy (LGMD) type 2B, the two most common dysferlinopathy phenotypes, corresponded to allelic disorders (Bashir et al., 1998; Liu et al., 1998; Illarioshkin et al., 2000). At present, more than 2000 polymorphic variants and over 260 disease-causing mutations associated with different dysferlinopathy phenotypes have been reported in the Leiden Muscular Dystrophy database (www.dmd.nl/dysf_seqvar.html), with the majority being point mutations and small insertions/deletions. Yet, many other non-pathogenic variants have also been included (Aoki et al., 2001). The exact incidence and prevalence of dysferlinopathy worldwide are unknown, but it has been estimated that it represents up to 30% of progressive recessive muscular dystrophies in the Middle East and India (Urtizberea et al., 2008).

In the present review, we discuss current evidence of the role of dysferlin in critical membrane related events, particularly in membrane repair and vesicle trafficking. We also discuss possible pathological mechanisms involved in dysferlinopathy, including the *de novo* expression of non-selective Ca^{2+} permeable channels, which might contribute to the inflammatory process associated to dysferlinopathy, and could provide readily accessible targets for pharmacological therapies.

2. Clinical background

Clinically, dysferlinopathy most commonly begins between the second and third decades in a previously asymptomatic patient. At onset, most patients complain of lower limb weakness, difficulties upon running or climbing stairs, sometimes aggravated by pain. These symptoms are usually accompanied by marked increase in plasma creatine kinase levels (CK) (Galassi et al., 1987; Barohn et al., 1991, 1998; Linssen et al., 1997; Rosales et al., 2010). Three main clinical phenotypes and some other variants of dysferlinopathy have been described (Miyoshi et al., 1967, 1986; Liu et al., 1998; Bashir et al., 1998; Illa et al., 2001; Nguyen et al., 2005, 2007; Laval and Bushby, 2004; Okahashi et al., 2008; Paradas et al., 2009; Klinge et al., 2008). There is also a marked inter- and intrafamiliar phenotypical variability (Miyoshi et al., 1986; Illarioshkin et al., 1996; Ueyama et al., 2002; Guglieri et al., 2008; Rosales et al., 2010, Woudt et al., 2016). However systematic muscle magnetic resonance imaging and functional assessment of patients with these different phenotypes do not show substantial differences in terms of distribution and severity of muscle compromise (Paradas et al., 2010; Díaz et al., 2016). After the first years of evolution, the disease mainly affects lower limbs, and later muscle weakness progresses involving paravertebral and proximal upper girdle muscles, to finally affect forearm flexor muscles. Head and neck muscles are not or very lately affected. Independent ambulation is lost on average after 10 years of disease course (Linssen et al., 1997; Woudt et al., 2016; Díaz et al., 2016). Although cardiac involvement is absent in most patients (Nguyen et al., 2007; Klinge et al., 2010a; Takahashi et al., 2013, Woudt et al., 2016), some recent evidences indicate that subclinical involvement is present in several patients with dysferlin deficiency (Wenzel et al., 2006; Choi et al., 2009; Rosales et al., 2010). So far, no central nervous system involvement has been described in dysferlin deficient patients, and respiratory involvement is mild, and presents itself in later stages of the disease (Takahashi et al., 2013; Woudt et al., 2016).

Dysferlin protein analysis is essential to confirm diagnosis, as the clinical features tend to overlap with other genetic disorders (i.e. mutations on calpain and caveolin-3 genes). Further, molecular analysis of the *DYSF* gene is most desirable in order to elucidate specific mutations that may relate to the disease (Bushby, 1999; Krahn et al., 2009). Clinical differential diagnosis of dysferlinopathy is mainly with other types of LGMD (Barohn et al., 1998; Bushby, 1999; Urtizberea et al., 2008; Guglieri et al., 2008; Fanin et al., 2009), as all LGMD patients may show a similar clinical picture. These include increased CK levels, weakness and wasting restricted to the limb musculature and relative sparing of heart and bulbar muscles (depending on the genetic subtype). This is particularly evident in LGMD type 2B and proximodistal dysferlinopathy; however, the combination of muscle atrophy of the posterior leg compartment and marked increase of CK levels in an adolescent or young adult is very suggestive of dysferlinopathy. To differentiate LGMD subtypes, immunohistochemistry and western blot are necessary in order to detect specific protein deficits and subsequently perform genetic analysis (Nguyen et al., 2007; Krahn et al., 2009; Fanin et al., 2009, Rosales et al., 2010). Genetic diagnosis after identification of the protein deficit is necessary to verify that this specific deficit is the cause of the dystrophy, and not secondary to mutations in other related genes (Krahn et al., 2009; Fanin et al., 2009, Rosales et al., 2010).

3. Dysferlin splice variants

The dysferlin gene is susceptible to suffer alternative splicing. In 2004, Salani and collaborators demonstrated that human primary myogenic cells express a dysferlin mRNA that lacks exon 17 and whose expression inversely correlates with muscle differentiation. This variant is later completely replaced by full-length dysferlin in adult skeletal muscle (Salani et al., 2004). Two years later, a novel human dysferlin transcript named DYSF_v1 was identified, which differs from the canonical dysferlin transcript in the sequence of the first exon (Pramono et al., 2006). The authors predicted that exon 1 of this new human dysferlin transcript shares 85% homology with the corresponding exon of mouse dysferlin and 89% with that of rat dysferlin. As in the canonical dysferlin, exon 1 of DYSF_v1 encodes for the first Ca^{2+}-binding domain (C2A), but, as discussed below, they differ in their Ca^{2+}-affinity (Fuson et al., 2014). Other dysferlin human transcript variants, produced by inclusions in exons 5a and 40a, were also reported (Pramono et al., 2009). All these variants could translate into different dysferlin isoforms, which as discussed later, appear to differ in their tissue distribution, sensibility to Ca^{2+}, and interaction with other proteins.

4. The ferlin family, a unique group of proteins with multiple C2 domains

Dysferlin belongs to the ferlin family, a group of single-pass transmembrane proteins that possess a short *C*-terminal extracellular domain and multiple (five to seven) tandem cytosolic C2 domains. These proteins also contain variable numbers of Fer and DysF domains. Fig. 1 shows how these different domains are organized in the ferlin family members dysferlin, myoferlin and otoferlin. Myoferlin is a mammalian ferlin highly expressed in developing skeletal muscle (Davis et al., 2000), where it is known to regulate myoblast fusion and muscle regeneration (Doherty et al., 2005). Myoferlin is also involved in membrane

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