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Spectrum of muscular dystrophies associated with sarcolemmal-protein genetic defects ☆

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ABSTRACT

Muscular dystrophies are heterogeneous genetic disorders that share progressive muscle wasting. This may generate partial impairment of motility as well as a dramatic and fatal course. Less than 30 years ago, the identification of the genetic basis of Duchenne muscular dystrophy opened a new era. An explosion of new information on the mechanisms of disease was witnessed, with many thousands of publications and the characterization of dozens of other genetic forms. Genes mutated in muscular dystrophies encode proteins of the plasma membrane and extracellular matrix, several of which are part of the dystrophin-associated complex. Other gene products localize at the sarcomere and Z band, or are nuclear membrane components.
In the present review, we focus on muscular dystrophies caused by defects that affect the sarcolemmal and subsarcolemmal proteins. We summarize the nature of each disease, the genetic cause, and the pathogenic pathways that may suggest future treatment options. We examine X-linked Duchenne and Becker muscular dystrophies and the autosomal recessive limb-girdle muscular dystrophies caused by mutations in genes encoding sarcolemmal proteins. The mechanism of muscle damage is reviewed starting from disarray of the shock-absorbing dystrophin-associated complex at the sarcolemma and activation of inflammatory response up to the final stages of fibrosis. We trace only a part of the biochemical, physiopathological and clinical aspects of muscular dystrophy to avoid a lengthy list of different and conflicting observations. We attempt to provide a critical synthesis of what we consider important aspects to better understand the disease. In our opinion, it is becoming ever more important to go back to the bedside to validate and then translate each proposed mechanism.

1. Introduction

The terms “progressive” or “pseudo-hypertrophic” muscular dystrophy appeared in the literature in the early 1900s. The definition “progressive muscular dystrophy of childhood” [1] was then adopted to indicate the least benign form of muscular dystrophy characterized by childhood-onset, X-linked inheritance, wasting and weakness of the muscles, and pseudo-hypertrophy of the gastrocnemius. At that time, genetic heterogeneity only consisted in a distinction with the facio-scapulo-humeral type showing autosomal dominant transmission [2]. The term “Duchenne-type” appeared at the end of the 1950s, after the re-discovery of papers dated 1868 of the great French neurologist Duchenne de Boulogne (1806–1875). This was not the first report, however, since Edward Meryon [3,4] and Gaetano Conte [5] had already published their work, in 1851 and 1836, respectively.

In 1985, Monaco and Kunkel identified distinct large deletions in the Xp21 region associated with Duchenne muscular dystrophy (DMD) [6]. For the first time they used the “reverse genetics” approach that searches for new genes from their chromosomal position without any prior functional data [7]. From the characterization of the DMD locus product, dystrophin [8], and its localization at the sarcolemma [9], a new era was opened and the dystrophin-associated protein complex was isolated and characterized [10–12]. A number of new sarcolemmal proteins were associated with other muscular disorders. Mutations of any of the four dystrophin-associated sarcoglycan subunits were associated with autosomal recessive limb-girdle muscular dystrophies (LGMD) [13–17], while mutations in the laminin α 2-chain gene (*LAMA2*) were associated with merosin-deficient congenital muscular dystrophy [18]. Alpha- and beta-dystroglycan were found to be central members the skeletal muscle dystrophin glycoprotein complex, linking dystrophin to proteins in the extracellular matrix. The intricate glycosylation steps that enable α-dystroglycan to interact with laminins, agrin and perlecan were further highlighted by the identification of about 15 neuromuscular disorders due to reduced dystroglycan glycosylation [19,20]. The dystrophin-associated complex may be considered as a functional entity with the role of reinforcing the plasma membrane during eccentric muscle contractions. Other muscular dystrophies are caused by mutations

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in genes encoding sarcolemmal proteins that operate in facilitating membrane re-sealing following injury, such as the dysferlin gene. Caveolin-3 deficiency, although sarcolemmal, is not included in this review, since it involves an alteration of vesicular trafficking that may be better associated with a distinct pathogenesis. Other non-sarcolemmal causes of LGMD have been recently reviewed [21].

1.1. Duchenne muscular dystrophy

Both the historical terms progressive and pseudohypertrophic are appropriate for Duchenne Muscular Dystrophy (DMD, MIM 310200). DMD has a childhood onset and a prevalence of 1 in 3,500 boys worldwide. Clinical symptoms of DMD are not present at birth. Diagnosis is usually made at 5 years of age, although serum enzymes derived from muscle membrane leakage (creatine kinase, transaminases, lactate dehydrogenase, aldolase) are extremely high since birth. Infants with serum creatine kinase levels above 2000 IU/l are 0.03% of the total population, but have high chance of being affected by DMD or LGMDs [22]. To reduce the diagnostic delay enabling earlier treatments, newborn screening has been considered [23] by taking a drop of blood from the heel of each child 24–48 hours after birth to test the level of creatine kinase.

Despite advances in diagnostic testing, the average age of diagnosis is 5 years, when the first clinical signs of DMD usually occur with a symmetrical weakening of the gluteal and quadriceps muscles. The most obvious consequence is a lordotic posture and difficulty in climbing stairs or in getting up from a squatted position. Classically, the child rises from the ground assuming a prone position with the arms on the quadriceps "climbing up" on himself (Gowers' maneuver). Total muscle force grows more slowly in DMD boys than their peers, and then begins to decrease starting from 7–8 years of age [24]. Weakness and joint contractures result in the loss of ambulation within 13 years. Typical, but non-specific for DMD, is the pseudohypertrophy of calves, associated with fatty infiltration of the soleus and gastrocnemius muscles. The weakness of the diaphragm and intercostal muscles as well as chest deformities leads to progressive reduction in vital capacity. Heart is often co-involved in the majority of patients [25]. It was recently reported that the prevalence of cardiomyopathy in 340 patients (aged 2–28 years) was 27% [26]. DMD boys show common reduced verbal ability with attention deficit: about 20% of cases present a more pronounced delay in learning and/or autistic behavior. Life expectancy has increased in recent years up to 40 years of age and this may be the result of improved management of respiratory and cardiac complications [27–29].

Becker muscular dystrophy (BMD, OMIM 300376) is apparently less frequent (1:11,500 males) than DMD, clinically milder, and more variable. BMD has later onset and a longer life expectancy. The gait may be waddling, although conserved until adulthood. BMD patients also show weakness of skeletal and respiratory muscles and dilated cardiomyopathy. There is also an X-linked dilated cardiomyopathy (XLDC), a condition characterized by exclusive cardiac dystrophin involvement [30].

2. Molecular genetics and testing

DMD and BMD are allelic muscular dystrophies caused by different mutations in the dystrophin (*DMD*) gene. This spans 2.22 Mb of DNA on the short arm of X-chromosome (Xp21) in a G-band, an A/T-rich region at low gene density. The *DMD* gene has in fact average-size exons separated by giant introns. Furthermore, the *DMD* gene has a high intragenic recombination rate of over 12 cM [31]. The *DMD* gene is so huge (the largest in the human genome) that each RNA molecule requires 16 hours of transcription [32], during which a co-transcriptional splicing generates a major mRNA species composed of 79 exons. Many non-coding RNAs are produced from the *DMD* locus, such as circular molecules of RNA [33] or long non-coding RNA [34]. There are at least four promoters at the 5' of the gene encoding a full-length dystrophin, while the internal promoters generate four shorter non-muscle isoforms, such as Dp260, Dp140, Dp116 and Dp71. The 14 kb-transcript is expressed in skeletal and cardiac muscle and, in smaller amounts, in the brain. It encodes for a rod-shaped dystrophin of 427 kDa [8,35]. DMD is caused by a category of mutations that make impossible to encode a functional dystrophin. Thus, the absence of dystrophin is the hallmark of DMD. BMD is more heterogeneous, since it is associated with distinctive gene defects that permit the synthesis of reduced amounts of qualitatively abnormal dystrophin. In addition to mini-dystrophins, maxi-dystrophins are also rarely observed. Compared with the 100% function of full-length dystrophin, these shorter isoforms should be in the functional range between 5% and 20%. Indeed, about 30% of full-length dystrophin is sufficient to avoid muscular dystrophy [36]. This indicates that some *DMD* gene defects with >30% of dystrophin can also be found in normal subjects [37]. Unlike the majority of other genes, large intragenic deletions account for ~65% of cases, and duplications for 10 %. These mutations are mainly located in two hotspots, the principal being at the 3' of the gene (exons 44–53) and the other at the 5' (exons 3–19). The largest database of dystrophin mutations can be found at www.dmd.nl [38]. Small mutations [39,40], consisting of nonsense mutations [41], insertions or deletions of a base and mutations of the splicing sites are relatively less frequent (23%). These are private and distributed throughout the cDNA, although mutations downstream of exon 74 are usually associated with BMD. As a rule, most point mutations in BMD affect splicing sites that allow a partial production of dystrophin [42]. The causative missense mutations mainly in the ZZ domain [43] are extremely rare, while a large number of amino acid variants of dystrophin are also found in healthy subjects. About 2% of DMD patients carry elusive mutations, such as deep intronic mutations or inversions. Deletions and duplications may be easily diagnosed in patients and carriers from peripheral blood DNA samples using quantitative techniques such as Log-PCR [44], MLPA [45,46] or custom array-comparative genomic hybridization [47–50]. The diagnosis of point mutations requires sequencing of cDNA from muscle biopsy, while for the use of next-generation sequencing (NGS) whole exome approach is justified only in the differential diagnosis [51]. To distinguish between BMD and DMD it may be important to check whether the residual frame mRNA is maintained after the deletion (Monaco's rule) [52]. The preservation of an open reading frame will allow the translation of a mini-dystrophin with a shortened rod domain. Even in the absence of unbalanced X inactivation, a heterozygous carrier of a mutation in the DMD gene may develop a cardiomyopathy [53].

3. Dystrophin

Dystrophin is a low abundance protein, accounting for approximately 75 mg/kg of muscle in healthy individuals (0.002% of the total striated muscle protein) [54]. Even if the amount of dystrophin is small, its role is crucial for the maintenance of muscle integrity. Dystrophin is a cytoskeletal protein located on the cytoplasmic side of the sarcolemma and forms a mechanically strong connection between the sarcolemma and the costameric cytoskeleton. This stabilizes cells by linking actin filaments, intermediate filaments, and microtubules to transmembrane complexes [55,56]. In dystrophin, we distinguish four functional domains: 1) the actin-binding domain: amino acids 14–240, (exons 2–8); 2) the large central rod-like domain consisting of 24 repeat units: aa 253–3040, (exons 8–61); 3) the cysteine-rich domain that binds β-dystroglycan: aa 3080–3360 (exons 62–69); 4) the unique C-terminal domain that interacts with dystrobrevin and syntrophins: aa 3361–3685 (exons 69–79). An additional binding site for actin is mapped in the middle of the rod [57]. Furthermore, spectrin-like repeats 16 and 17 (R16/R17) of the rod domain can bind nNOS [58,59]. This observation suggests that not only α1-syntrophin [60,61], but also dystrophin directly contributes to the sarcolemmal localization of nNOS [58].

Dystrophin is part of a large protein complex, the dystrophin-glycoprotein complex (DGC). Dystroglycan is the central protein of

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DGC. It spans the sarcolemma and binds to ligands in the surrounding basal lamina through α-dystroglycan and to dystrophin inside the cell through β-dystroglycan. The glycosylated α-dystroglycan binds laminin-211 [62] in the extracellular matrix and completes the bridge of muscle stability. α-, β-, γ-, and δ-sarcoglycan, α-dystrobrevin, syntrophins and sarcospan are essential components of DGC (Fig. 1).

4. Sarcoglycanopathies

Mutations in several components of DGC and other constituents associated with muscle membrane are the cause of other forms of inherited muscular dystrophy or congenital muscular dystrophies.

The sarcoglycans are single transmembrane domain-containing proteins that are N-glycosylated on their larger extracellular domain. Post-translational processing of the sarcoglycan complex is necessary for proper functioning of DGC. Each sarcoglycan is glycosylated on asparagine residues, whereas nonglycosylated forms of β- and δ-sarcoglycan fold incorrectly, mislocalize and aggregate. The genes involved in their glycosylation are still unknown. Sarcoglycan proteins form a heterotetrameric complex linked to the dystrophin-dystroglycan axis [63]. Autosomal recessive LGMDs 2C-2F are caused by primary mutations in any of four genes encoding sarcoglycan complex subunits: LGMD2C (γ-sarcoglycan) [15], LGMD2D (α-sarcoglycan) [16], LGMD2E (β-sarcoglycan) [13,17], and LGMD2F (δ-sarcoglycan) [14,64]. There are two other non skeletal muscle sarcoglycans: ε-sarcoglycan, which is mutated in myoclonus dystonia [65] and ζ-sarcoglycan [66], which is homologous to γ- and δ-sarcoglycan, only expressed in brain and cerebellum.

Assembly of the sarcoglycan complex in skeletal muscle has been studied *in vivo* and *in vitro* [11]. The sarcoglycan core is formed by the basic proteins β- and δ-sarcoglycan that are assembled first, followed by the inclusion of γ-sarcoglycan and then α-sarcoglycan. In the smooth muscle, the sarcoglycan complex contains the ε-sarcoglycan instead of α-sarcoglycan, while in the heart the sarcoglycan complex comprises both types. The complete sarcoglycan complex then associates with the dystroglycan complex and sarcospan, and is delivered to the membrane apparently through vesicular transport along microtubule networks [67]. Synthesis of dystrophin occurs independently and this is consistent with the observation that dystrophin is present even in the absence of the sarcoglycan complex.

In case of a mutant sarcoglycan that fail to pass quality control in the endoplasmic reticulum (ER), it will be dislocated into the cytosol and degraded by the proteasome. Unlike others, α-sarcoglycan may be able to translocate alone to the plasma membrane after leaving the Golgi [68]. When disease is only caused by mislocation of α-sarcoglycan, targeted drugs may theoretically be used to rescue LGMD2D [69]. In contrast, when β-sarcoglycan or δ-sarcoglycan are absent, no sub-portions of the sarcoglycan complex are found at the sarcolemma. Muscle biopsies of patients with some missense mutations of α-sarcoglycan show only a reduction of the remaining sarcoglycans, β-, γ-, and δ-. Presence of β-, α-, and δ-sarcoglycan may also occur with some mutations of γ-sarcoglycan. When the sarcoglycan complex is absent from the skeletal muscle, dystrophin is only minimally affected. However, dystrophin absence is followed by a marked reduction of the sarcoglycan complex at the sarcolemma. This reduction of sarcoglycan is also seen in the *mdx* mouse, a naturally occurring spontaneous mutant that serves as a model of DMD. In mouse model of α-sarcoglycan deficiency, the cardiac sarcoglycan complex and the dystrophin-dystroglycan are mildly reduced, unless the ε-sarcoglycan is also lacking [70]. The sarcoglycanopathies are typically forms of LGMDs with childhood onset. Mutations in any of the four sarcoglycan genes (sarcoglycanopathies) constitute about 10-15% of all LGMD2s [63,71,72], but 68% of the severe forms [73]. LGMD2D is the most prevalent, but LGMD2C is common in the Maghreb and India [74] for the high allele frequency of 525delT and in Gypsies for the Cys283Tyr allele [75]. The clinical profile of sarcoglycanopathies is heterogeneous with both severe and mild forms, which are also found in the same families [76]. In general, the disease is more severe and rapid than in other LGMDs. The typical form has a childhood onset usually with quadriceps muscle wasting. Cardiomyopathy may occur in all forms [77,78], but rarely in LGMD2D. In animal models, δ-sarcoglycan mutations are associated with cardiomyopathy [79,80].

DMD and sarcoglycanopathies share the sarcoglycan loss, which is primary and secondary, respectively. Mouse models have helped to understand whether the loss of sarcoglycan is a key step for membrane instability and whether the restoration of the sarcoglycan complex alone may be useful to prevent muscular dystrophy.

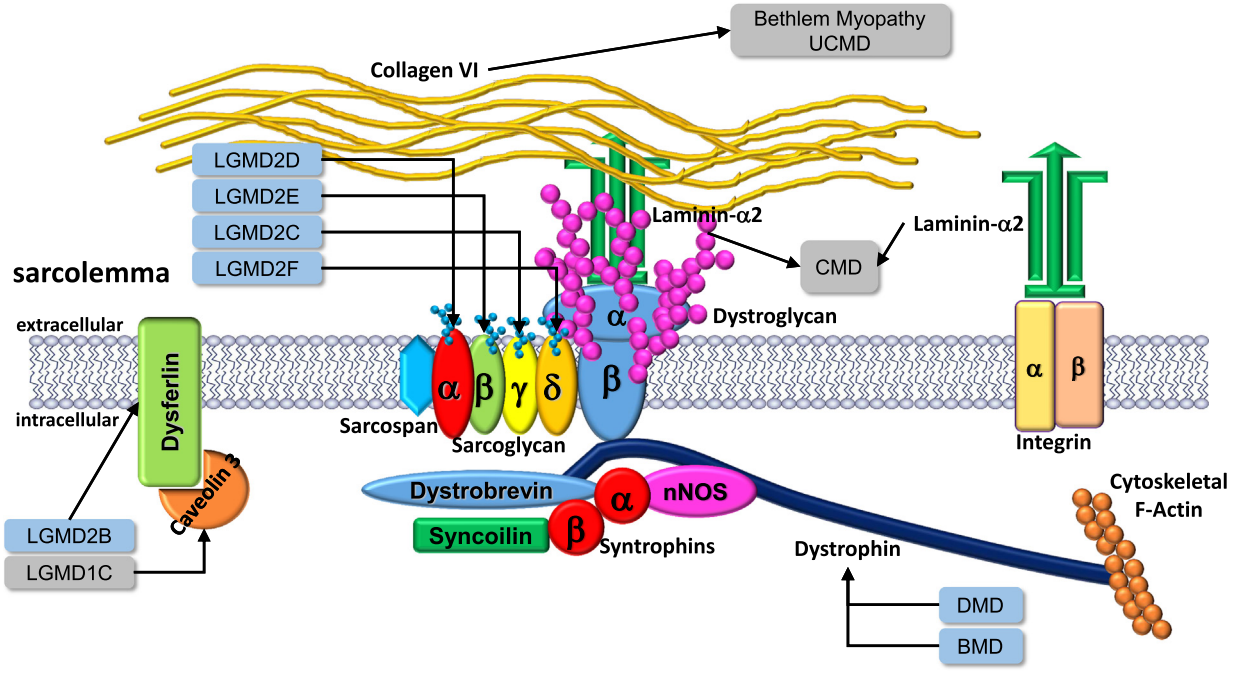

Fig. 1. Schematic representation of dystrophin-glycoprotein complex (DGC) and of other sarcoplasmic associated proteins involved in muscular dystrophies.

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A transgenic mouse overexpressing the dystrophin short form Dp260 in the *mdx* dystrophin-deficient background was generated [81]. The overexpression of Dp260 was important for costameric assembly of the dystrophin-glycoprotein complex, including sarcoglycan and dystroglycan, but the mice presented the same reductions in force generation of *mdx* muscles. These data suggest that when the DGC is present and properly localized, it provides protection from contraction-induced injury, but this is not sufficient to prevent the dystrophic process in the lack of the N terminus of dystrophin, which may have a second nonmechanical function. Increased muscle mass and total force were obtained with the overexpression of a shorter form of dystrophin, Dp116, in the skeletal muscle of severely affected dystrophin/utrophin gene double knock-out mice [82]. Although this animal model is very prone to spectacular phenotypic rescues with many other treatments, these data indicate that the lack of dystrophin may damage two separate functions: i) the assembly of DGC (sarcoglycan and dystroglycan), which is critical for growth and maintenance of muscle mass; ii) a linkage between the extracellular matrix and the actin cytoskeleton, which is able to prevent dystrophic pathophysiology.

5. Dystroglycanopathies

Dystroglycan is produced as a single polypeptide from the *DAG1* gene that is subsequently cleaved into α- and β- subunits at residue 653. α/β-dystroglycan is not only a protein of DGC, but is mostly associated in nonmuscle tissues with other extracellular matrix proteins. It appears that even in muscle a significant fraction of dystroglycan does not directly associate with dystrophin or utrophin (dystrophin homolog), but is part of separate protein complexes distinct from DGC [83]. The absence of dystroglycan is embryonically lethal in mice due to the disruption of Reichert's membrane [84]. For a review of the numerous roles of dystroglycan see [85].

One single missense mutation in the dystroglycan gene causing LGMD2P has so far been identified [86,87]. Recent advances have highlighted the importance of post-translational processing for the interaction of dystroglycan with its ligands. A very large number of muscle and brain disorders are, in fact, caused by mutations in genes that are directly or indirectly responsible for the glycosylation of α-dystroglycan and studies on these conditions have provided insights into its crucial steps. Dystroglycan undergoes both asparagine (N)-linked and serine/threonine (O)-linked glycosylation as part of its normal processing. There are three N-linked glycosylation sites on α-dystroglycan and approximately 50 O-linked glycosylation sites. Most dystroglycanopathies are associated with hypoglycosylation of α-dystroglycan, which can be seen in both muscle and brain. Mutations in many genes cause secondary dystroglycanopathies. *POMT1*, *POMT2* and *POMGnT1* encode proteins involved in the mannosylation of serine or threonine residues of α-dystroglycan by means of an O-linkage [85]. *FKTN*, *FKRP* and *GTDC2* encode glycosyltransferases on the basis of sequence homology. The *DPM1* [88], *DPM2* [89], and *DPM3* [90] genes encode subunits of the dolichol-phosphate-mannose (DPM) synthase. DOLK encodes dolichol kinase responsible for formation of dolichol-phosphate and its mutations cause dilated cardiomyopathy [91]. *LARGE* encodes for a bifunctional enzyme, the Like-acetylglucosaminyltransferase. Interestingly, expression of LARGE strongly enhances the laminin binding activity of α-dystroglycan. For this reason, its up-regulation has been claimed to be one of the most promising possible therapies for muscular dystrophy [92,93]. However, recent data indicate that there is a worsening of muscular dystrophy [94,95]. *B3GNT1* and *B3GALNT2* code for new glycosyltransferase. Finally, mutations in the *ISPD*, *TMEM5* and *GMPPB* genes also cause dystroglycanopathies [20].

In humans, mutations affecting the glycosylation of dystroglycan result in disorders such as congenital muscular dystrophies, muscle-eye-brain disease (MEB), and Walker-Warburg syndrome (WWS). From a clinical point of view, dystroglycanopathies may be very severe conditions in which syndromes include severe malformations of the brain and eye. There is also the possibility of milder muscular phenotypes associated with mutations of the same genes. In genotype/phenotype correlation it is crucial to take into account the residual enzyme activity of the mutated gene product. A severe or lethal phenotype may be observed in the case of homozygosity for null alleles [19]. Alternatively, the presence of hypomorphic alleles, consisting of amino acid substitutions that do not completely inactivate the enzyme activity, confines the clinical profile to skeletal muscle, milder and classified as LGMD. The most frequent LGMD gene in this group is *FKRP*, which causes LGMD2I. In some countries (UK, Denmark, and Norway) LGMD2I is relatively common, for the high carrier frequency of the Leu276Ile allele (1:116). LGMD2I may be clinically similar to BMD, with a late-childhood onset, calf hypertrophy, high serum CK, and cardiomyopathy and respiratory impairment that may prevail.

6. Dysferlinopathy

Dysferlin is a sarcolemmal protein that may be deficient in a form of LGMDs (LGMD2B). LGMD2B is the second form in order of frequency (about 15–25%) in many geographical areas [96–98], but not everywhere [99]. Dysferlin is a ubiquitous 230-KDa transmembrane protein involved in calcium-mediated sarcolemma resealing [100]. Although muscle inflammation is widely recognized in dysferlinopathy and dysferlin is well expressed in monocytes, the role of the immune system to the pathology remains obscure. Muscle of dysferlinopathy patients is characterized by massive immune cell infiltrates, and dysferlin-negative monocytes were shown to be more aggressive, but macrophages show altered adhesion and motility [101]. *DYSF* mutations are associated with mixed clinical presentations including severe functional disability to mild late-onset forms [102,103]. About 25% of cases may be clinically misdiagnosed as having polymyositis [104]. The same mutations cause a distal myopathy, known as Miyoshi myopathy type 1 (MM1) [105]. However, classification of separate clinical phenotypes is more apparent than real and is not justified by pathological differences [106].

Some patients were very athletic before the onset of symptoms [107] and this suggests that a competitive physical activity may modify the penetrance of *DYSF* mutations. Regeneration seems to be attenuated [108]. Dysferlin has a crucial role in muscle repair [109] and this will promote strategies to facilitate membrane resealing in dysferlinopathy [110].

7. Mechanisms of muscle damage

The biochemical cause of DMD is the absence of a functional dystrophin, which results in the reduction or complete absence of the remaining DGC components from muscle membrane, and disarray of the shock-absorbing connection at the sarcolemma. Furthermore, the loss of DGC-actin axis causes a threefold decrease in muscle elasticity in mice [111,112]. This destabilizes the transmission of lateral force, boosting the number and size of sarcolemmal micro-tears mainly caused by lengthening (eccentric) muscle contractions [113] (Fig. 2A). This explains why large and non-hydrophobic muscle proteins can traverse the lipid bilayer and increased serum activities are detected. In normal subjects, micro-tears are typically associated with inflammation and elayed onset muscle soreness [114]. In normal muscle regeneration, any transient inflammatory response is followed by the activation and proliferation of myoblasts that differentiate into myocytes, and fuse to form myofibers, typically with centralized nuclei, resulting in repair. In general, micro-tear formation and repair of the lipid bilayer also occur repeatedly in DMD, but with time, they eventually produce degeneration of the muscle fiber. In this case, the inflammatory response becomes chronic and damaging.

There is general agreement on the hypothesis of $Ca2+$ ion entry into the cytoplasm through micro-tears and probably through active calcium channels [115,116] (Fig. 2B). Mice overexpressing transient receptor potential canonical 3 (TRPC3) develop biochemical signatures of myofiber degeneration and regeneration, infiltration of immune cells, and fibrosis, suggesting that lifelong $Ca2+$ increase may induce some

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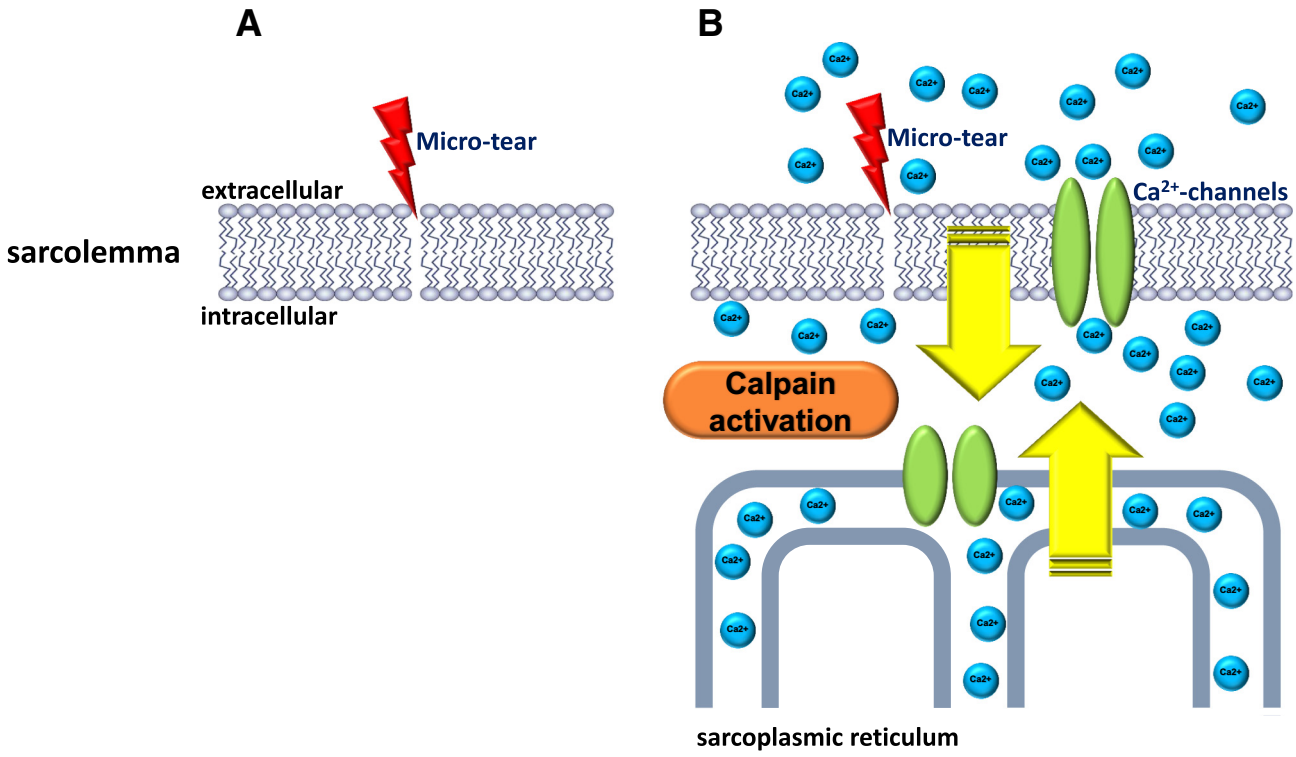

Fig. 2. Sarcolemmal micro-tears (A) concur with sarcoplasmic reticulum leaking (B) in determining Ca2 + ions influx.

dystrophic-like pathways [117]. Increased calcium concentration or functional ischemia from the loss of nNOS at the sarcolemma could explain why DMD children may suffer from nocturnal muscle cramps after major daily movements. Calcium entry will activate calpains and perturb the homeostasis of muscle proteins leading to fiber degeneration and death. Although overexpression of the calpain inhibitor, calpastatin, may reduce the dystrophic process in *mdx* mice [118], it is simplistic to consider proteolysis by calpain as directly responsible for muscle atrophy, since many other mechanisms remain to be clarified. Fibers may undergo necrosis by excessive calcium influx and this triggers key damage pathways that progress towards the progressive replacement of affected muscle with connective and adipose tissue.

Claims about the key pathways that precede and/or promote muscular dystrophy involve abnormal signaling, oxidative stress, inflammatory response, autophagy dysregulation, apoptosis, and fibrotic response.

All these studies may have some intrinsic limitations such as the biochemical methods applied to cells that cannot explain working-muscle physiology and preferential damage in some muscles. In addition, the widely used *mdx* mouse is only dystrophin-deficient, but not affected by DMD. *Mdx* mouse muscle shows a higher regenerative capacity that ensures a more benign phenotype and essentially normal function. Some pathways are not shared, such as the activation of calcineurin/NFAT pathway [119], which is not active in DMD [120] together with other important differences [121].

The first claim to be proved is the additional roles of dystrophin and the glycoproteins as signaling molecules [122]. The claim derives from the early alteration of many signaling pathways in DMD [123]. Aberrant signaling eventually results in altered myogenic expression and pathology in muscular dystrophy, but it is difficult to distinguish between causes and effects.

Nitric oxide (NO) is a signaling molecule that regulates different skeletal muscle functions, such as force production, the maintaining of an adequate blood flow during contraction, respiration and glucose homeostasis [124]. In DMD patients and dystrophic animal models, the loss of DGC integrity delocalizes nNOS from the sarcolemma and it appears diffusely reduced in the cytosol [125–127]. As previously discussed, the R16/17 spectrine-like motifs within rod domain concur with syntrophin to the sarcolemmal localization of nNOS [58–61]. A most severe phenotype has been observed in BMD patients carrying deletions of exons encoding R16/17 motifs within rod domain [128–130]. Therefore, nNOS mislocalization greatly contributes to the dystrophic phenotype by inducing functional ischemia [131–133], by impairing satellite cell activation and by increasing fatigue-mediated injury, as well as by increasing oxidative stress and inflammation [134,135].

However, little doubt remains as to the importance of the inflammatory response in muscular dystrophy. Neutrophils, macrophages and T cells infiltrate muscle at stages that anticipate the onset of clinical disease. Inflammation never stops, but persists until muscle tissue is present. Inflammation may be considered as the central process that contributes to muscle lesion formation and progression. In particular, the balance between proinflammatory macrophages M1 and anti-inflammatory macrophages M2 is critical for the degeneration/regeneration of muscle (Fig. 3). In muscular dystrophy, the resident mononuclear phagocyte populations cannot adequately respond to tissue stress and waves of recruitment of monocytes enter the injured muscle and differentiate into a spectrum of mononuclear phagocytes. The newly recruited cells are proinflammatory and secrete pro-inflammatory mediators such as tumor necrosis factor (TNF), nitric oxide (NO) and IL-1. Other mediators produced by activated macrophages include IL-12 and IL-23, which are decisive in influencing the polarization of TH1 cells, which further drive inflammatory responses forward. Furthermore, macrophages can cause phagocytosis of injured myofibers and then present antigens to T cells to induce their activation. Activated macrophages produce reactive oxygen and nitrogen intermediates, including NO and superoxide, which are toxic for neighboring tissues and lead to aberrant inflammation. Indeed, M1 macrophages must be limited to avoid extensive tissue damage, while M2 macrophages exhibit potent anti-inflammatory activity and have important roles in wound healing and fibrosis (Fig. 3). M2 macrophages also antagonize M1 responses, which may be crucial for wound healing and restoration of muscle tissue stimulating the proliferation of satellite cells [136]. TNF-α and IFN-γ are two inflammatory cytokines produced by both M1 macrophages and skeletal muscle cells that inhibit transition

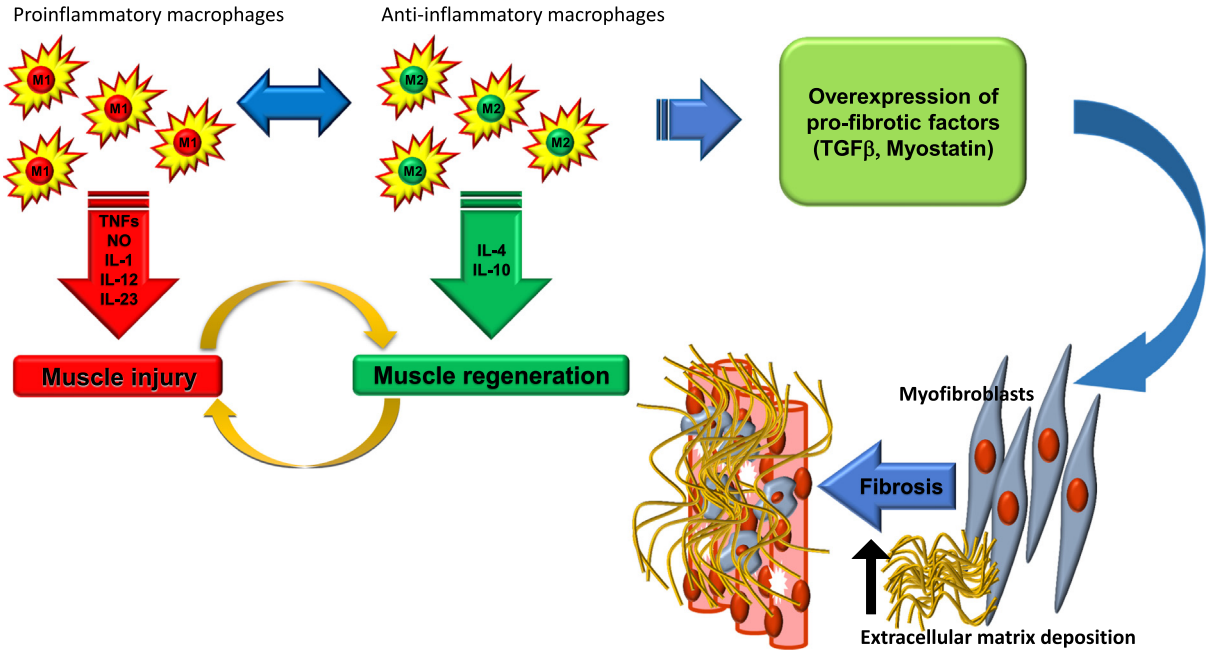

Fig. 3. The role of M1 and M2 macrophages in muscle injury and regeneration, as well as in promoting fibrosis.

from M1 to M2 phenotype. In contrast, anti-inflammatory cytokines such as IL-4 and IL-10 promote activation of M2 macrophages in the form of M2a and M2c [136]. Accordingly, treatment of *mdx* mice with IL-10 improved the histological features by deactivating M1 macrophages and promoting regeneration [137,138], while genetic ablation of the *IL10* gene caused extensive infiltrates of pro-inflammatory M1 macrophages in *mdx* mice with major cardiac and respiratory dysfunction [139].

These immune response-related aspects could be associated with the clinical benefits produced by the use of steroid in DMD. Steroids are used worldwide to improve muscle strength, increase muscle mass, and slow the progression of the disease [140,141]. Nevertheless, the mechanism of action of steroids in dystrophin deficiency is well beyond their role in immune response, involving membrane effects and multiple levels of regulation [142,143]. The over-simplified equation "stronger immune response/more dystrophy" has promoted other immunosuppressive approaches to treat DMD. However, an important clinical trial using cyclosporin A for treatment of a large number of DMD boys did not show any significant improvement in primary outcome measures and no major improvement in pathology [144,145].

The fatal destiny of muscular dystrophy is the commitment towards the progressive fibrosis that impairs any residual muscle force and elasticity. In addition, fibrosis affects the vital functions and is the major problem for future treatments based either on stem cell or gene delivery. Fibrosis occurs as the outcome of a chronic inflammation process and necessarily involves the TGFβ pathways [146] (Fig. 3). However, inflammatory response and overexpression of proteins such as transforming growth factor-beta1 (TGF-β1) and myostatin, promote the formation of fibrotic tissue to replace damaged myofibers. Drug targeting of the TGFβ pathways is, promisingly, within reach [147]. Genetic background can also modify the fibrotic response, such as polymorphisms of the latent TGFβ binding protein 4 gene (*LTBP4*) [148]. Recently, it has been demonstrated that fibro-adipogenic progenitors may choose to support muscle regeneration or promote fibro-adipogenic degeneration and that HDAC inhibitors may de-repress a latent myogenic program in young *mdx* mice [149].

8. Conclusions and promises

Within the DGC, the sarcoglycan complex, α/β-dystroglycan and dystrophin are interconnected at multiple levels including post-translational processing, trafficking to the membrane and during their more stable interaction at the membrane. Mutations in genes that are part of this complex affect the muscle stability.

Genetic and stem cell therapy approaches are being pursued in animal models of muscular dystrophies [150]. The sarcoglycanopathies are at the forefront of experimenting with gene therapy protocols using adeno-associated viruses (AAVs), because cDNAs are all small in size and, most importantly, they work in animal models [151] including the four KO mice and BIO14.6 cardiomyopathic hamster (δ –sarcoglycan deficient) [79]. Micro-dystrophin has been successful delivered through AAV into dystrophic dogs [152].

For DMD, one encouraging advance has been the targeting of RNA of dystrophin by antisense oligonucleotides to induce exon skipping in boys with out-of frame deletions [153]. The strategy aims to restore the open reading frame and generate minidystrophins (BMD-like). This has progressed rapidly to phase 3 clinical trials [154]. Similar approaches are being explored in other genetic disorders, such as myotonic dystrophy, dysferlinopathies, and motor neuron diseases [155].

Numerous pharmacological approaches that interfere with the secondary processes involved in dystrophic progression are effective in preclinical models and many drugs are under study. These efforts will raise more hopes for muscular dystrophy patients.

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