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REVIEW

Costamere proteins and their involvement in myopathic processes

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Muscle fibres are very specialised cells with a complex structure that requires a high level of organisation of the constituent proteins. For muscle contraction to function properly, there is a need for not only sarcomeres, the contractile structures of the muscle fibre, but also costameres. These are supramolecular structures associated with the sarcolemma that allow muscle adhesion to the extracellular matrix. They are composed of protein complexes that interact and whose functions include maintaining cell structure and signal transduction mediated by their constituent proteins. It is important to improve our understanding of these structures, as mutations in various genes that code for costamere proteins cause many types of muscular dystrophy. In this review, we provide a description of costameres detailing each of their constituent proteins, such as dystrophin, dystrobrevin, syntrophin, sarcoglycans, dystroglycans, vinculin, talin, integrins, desmin, plectin, etc. We describe as well the diseases associated with deficiency thereof, providing a general overview of their importance.

Introduction

The concept of the costamere as a morphological structure in striated muscle was first introduced by Pardo et al. in 1983 (Ref. 1). The observation under an electron microscope of protein bands perpendicular to the longitudinal axis of the muscle fibre, reminiscent of ribs ('costa' in Latin), led them to coin the name costamere (Ref. 1). It was found that these structures are located at the subsarcolemmal level, aligned with the myofibril Z-discs (Refs 1, 2, 3). Similar structures are oriented transversely over the M lines of the contractile apparatus and oriented parallel to the long axis of the myofibre (Ref. 4) (Fig. 1).

Functions of costameres

Possible functions of costameres may include the assembly and stabilisation of sarcomeres (Refs 1, 5, 6). Specifically, these protein complexes, associated with the sarcolemma, enable muscle adhesion to the extracellular matrix (Ref. 7) and provide mechanical linkage. This linkage both distributes contractile forces from the sarcomere to the basal lamina ('inside-out') (Refs 5, 6) and transmits externally applied forces to the extracellular matrix inside the myocytes ('outside-in') (Ref. 8). Given this, it could be expected that defects in costameres would compromise muscle strength directly. These defects would reduce the efficiency of the transmission of lateral forces, and/or indirectly, increase the likelihood of damage to the sarcolemma, resulting in degeneration or death of the myofibre (Ref. 4).

The process of sarcomere assembly is complex and remains poorly understood (Ref. 9). In the initial stages of assembly, there are small aggregates associated with the membrane, known as Z-bodies, which will mature into Z-discs (Ref. 10). Integrins, α-actinin and the constituents of binding sites for integrin, vinculin and talin are the first proteins that can be observed with a periodic pattern in the plasma membrane (Refs 11, 12). There is abundant evidence suggesting that integrin-binding sites are where myofibril assembly starts in vivo. Sparrow and Schock (Ref. 13) suggested that, within the myofibril maturation process, protocostameres are the site of early integrin binding and, hence, of the initiation of myofibril assembly, although other authors proposed an alternative model based on the assembly of multiple latent protein complexes (Ref. 9).

The correct alignment of costameres with the Z- and M-lines is dependent on other structures in the network of filamentous proteins of the cytoskeleton, namely, the family of the intermediate filaments (IFs) (Refs 14, 15). These are responsible for binding between the sarcolemma and the myofibrils adjacent to the Z-lines (Refs 16, 17, 18) and presumably also the M-lines (Refs 16, 19). Desmin, together with other associated proteins, synemin and paranemin, form the IFs of the Z-lines (Refs 20, 21) (Fig. 1). The complex process

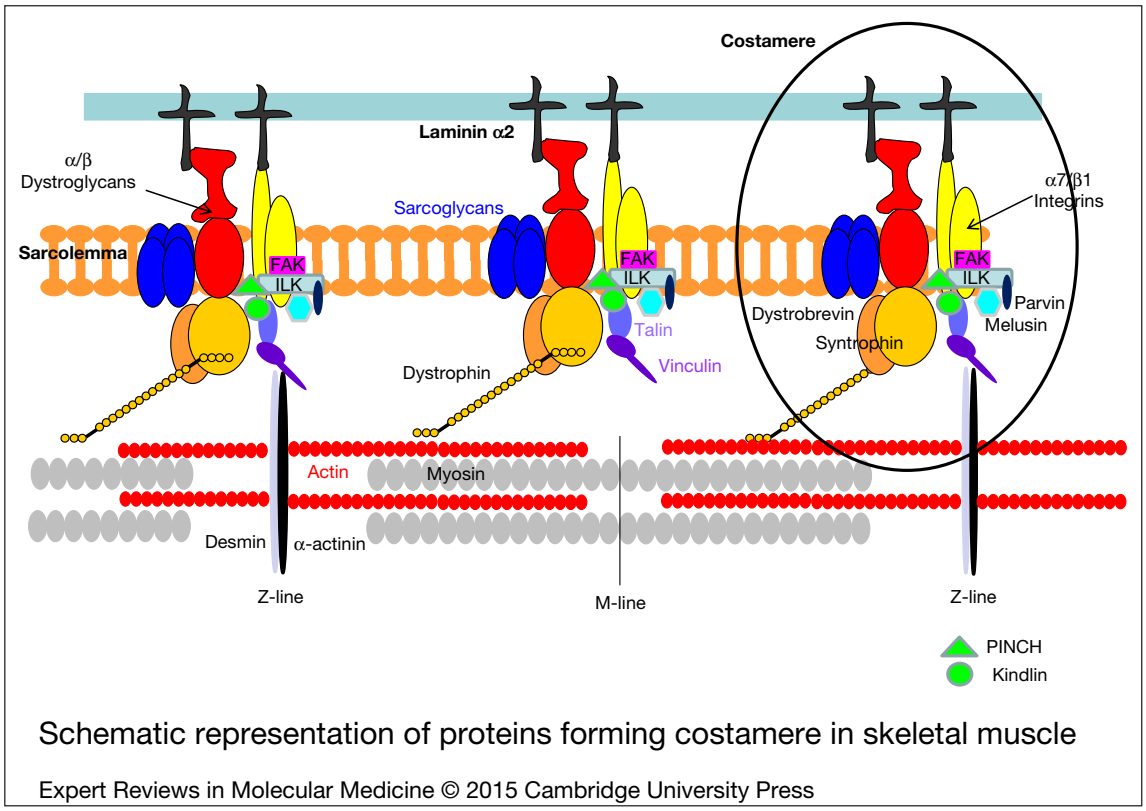

FIGURE 1

Schematic representation of proteins forming costamere in skeletal muscle. FAK, focal adhesion kinase; ILK, integrin-linked kinase; PINCH, particularly interesting cysteine- and histidine-rich protein.

of assembly is genetically regulated by a specific process that involves transcription factors: myocyte enhancer factor-2 (MEF2), serum response factor (SRF) and histone deacetylase (Ref. 22).

First, MEF2 is a transcription factor (Refs 23, 24, 25) required for the terminal differentiation of cardiac, skeletal and smooth muscle (Refs 26, 27, 28). MEF2A, in particular, plays an essential role in muscle regeneration in adult mice through direct regulation of the microRNA cluster, the Gtl2–Dio3 locus. A subset of the Gtl2–Dio3 miRNAs represses secreted Frizzled-related proteins, inhibitors of Wnt signalling (Ref. 29). Second, SRF is a broadly expressed transcription factor with an essential role in the differentiation of mesoderm-derived tissues, such as muscle (Ref. 30). In floxed SRF mice, there is dysregulation of genes encoding costamere, sarcomere and numerous other cytoskeletal proteins (Ref. 31), such as dystrophin, α-dystrobrevin, integrin β1, melusin and β-sarcoglycan (Ref. 22).

As well as gene regulation through transcription factors, mechanical stimuli play an important role in regulating the expression of costamere components (Refs 32, 33, 34, 35, 36), their level of expression also varying between fibre types (Refs 17, 37, 38, 38, 39, 40, 41).

To summarise, the assembly of sarcomere proteins is a highly regulated, complex and delicate process, depending on many factors, and abnormalities in these factors, for example, as a result of mutations of genes coding for some of their components, produce a range of different myopathic processes (listed in Table 1). Below, we describe the main constituent proteins of costameres, their location within the cell and their involvement in these myopathic processes.

Main components of costameres

Costameres are principally composed of two complexes, the dystrophin–glycoprotein complex and the vinculin–talin–integrin system. Both regulate the interaction between the cytoskeleton and the extracellular matrix in skeletal muscle in adults (Ref. 42).

The intracellular actin fibres, which are part of the contractile apparatus, are bound to laminin of the extracellular matrix by dystrophin (Refs 43, 44, 45, 46). Integrin α7β1, a transmembrane laminin receptor, also helps to link the extracellular matrix and the cytoskeleton (Refs 47, 48, 49) (Fig. 1).

In addition to the aforementioned two complexes, other proteins, including desmin, plectin and melusin, are involved and these are described in more detail below.

The dystrophin–glycoprotein complex (DGC)

This structural unit is composed of dystrophin and a series of proteins (dystroglycans α and β, sarcoglycans

TABLE 1
MUSCLE DISORDERS BECAUSE OF MUTATIONS OF GENES CODING COSTAMERE COMPONENTS

Gene/protein	Myopathic features	Allelic variants or associated (extended) phenotypes
1- Dystroglycan complex (DGC)		
1.1. Sarcoplasmic subcomplex		
DMD **Dystrophin**	Progressive proximal muscular weakness with characteristic pseudohypertrophy of the calves and cognitive impairment. Bulbar (extraocular) muscles spared but the myocardium is affected. Massive elevation of creatine kinase levels in the blood, myopathic changes by electromyography, and myofibre degeneration with fibrosis and fatty infiltration on muscle biopsy	Duchenne muscular dystrophy (DMD), because of the total absence of dystrophin. Onset occurs between 3 and 5 years of age with a progressive loss of muscle strength. Patients stop being able to walk at 11–13 years old and die around the 3rd decade of life, often because of respiratory failure (Refs 45, 55, 145) Becker muscular dystrophy (BMD) is an allelic variant, in which patients have mutations in the dystrophin gene. Deletions identified in BMD patients are shown to maintain the translational ORF for amino acids and predict a shorter, lower molecular weight protein. The smaller protein product is presumed to be semifunctional and to result in a milder clinical phenotype (Refs 146, 147) X-linked dilated cardiomyopathy (or dilated cardiomyopathy 3B), secondary to mutations in dystrophin coding gene (Ref. 148) Intermediate muscular dystrophy, a phenotype between DMD and DMB (Ref. 149) Asymptomatic carriers and symptomatic female carriers (Refs 150, 151)
DTNA **Dystrobrevin**	–	Noncompaction of left ventricular myocardium with congenital heart defects (Ref. 62) Autosomal-dominant familial Meniere's disease (Ref. 152)
STNA1 **Syntrophin**	–	Case of a patient with long QT syndrome with a mutation in the gene coding for α−1 syntrophin (STNA1) (Ref. 67)
1.2. Sarcoglycan subcomplex		
SGCA, SGCB, SGCG, SGCD and *SGCZ* **α, β, γ, δ, ε and ζ-sarcoglycans**	Slowly progressive proximal muscle weakness impeding patients' ability to walk during adolescence in most cases. Similar clinical picture to DMD with an onset in childhood, but broader clinical spectrum and onset in adulthood in some cases	Limb-girdle muscular dystrophy (LGMD) 2C: γ-sarcoglycanopathy (Ref. 73), common in Maghrebian populations (Ref. 153, 154) and among gypsies (Ref. 155) LGMD2D: caused by mutations in the α-sarcoglycan gene (Ref. 156) LGMD2E: caused by mutations in β-sarcogycan coding gene are responsible for LGMD2E (Ref. 157) This LGMD was found in affected members of several Amish families (Ref. 158) LGMD2F: δ-sarcoglycanopathy (Ref. 159) As well as LGMD2F, mutations in the gene coding for δ-sarcoglycan may lead to dilated cardiomyopathy 1L (CMD1L) (Ref. 160) Mutations in the gene coding for ε-sarcoglycan (SGCE) have also been described in patients with myoclonus-dystonia syndrome (Ref. 161) No disorders have been associated with the gene that codes for ζ-sarcoglycan (Ref. 162)
1.3. Dystroglycan subcomplex		
DAG1 **Dystroglycan 1**	Girdle myopathy affecting the central nervous system	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C9, muscular dystrophy-dystroglycanopathy (limb-girdle), type C9 (Ref. 79) Abnormal glycosylation of DAG1 results in several forms of congenital muscular dystrophy, ranging phenotypically from severe forms with brain and eye anomalies to milder limb-girdle types, for further information please see http://www.musclegenetable.fr
2- Vinculin-talin-integrin system		
VCL **Vinculin**		Dilated cardiomyopathy type 1W (Ref. 88) Familial hypertrophic cardiomyopathy-15 (Ref. 89)
TLN1/*TLN2* **Talin**	–	
ITGA7 **Integrin α7** *ITGA9* **Integrin α9**	Congenital myopathy with hypotonia	Integrin α7-deficient congenital muscular dystrophy: Mild congenital myopathy with delayed motor milestones. Torticollis and congenital dislocation of the hip. Intellectual impairment in one case (Ref. 99) Congenital muscular dystrophy with joint hyperlaxity: Patients hypotonic and present contractures at birth. Muscle weakness is generalised and slowly progressive. Contractures are proximal at the ankle, knee and shoulder (Ref. 100)

Continued

Table 1 *Continued*

Gene/protein	Myopathic features	Allelic variants or associated (extended) phenotypes
COL6A1 *COL6A2* *COL6A3* **Collagen VI**	Muscle weakness and contractures, associated with variable degrees of joint hyperlaxity	Ullrich congenital muscular dystrophy (UCMD), the most severe form of collagen VI disorders, is characterised by early onset and proximal joint contractures associated with striking distal hyperlaxity. The orthopedic deformities and respiratory impairment, with diaphragm failure, generally develop within the first decade of life and are life-threatening in the most severe cases (Ref. 103) Bethlem myopathy (BM) characterised by early contractures of finger flexors, wrist, elbows and ankles. Respiratory failure and distal hyperlaxity are usually absent or are milder than in UCMD, although the latter may occur only in very young children with BM (Refs 103, 104) Myosclerosis myopathy (Ref. 105)
3- Other proteins associated with costameres		
3.1. Integrin-associated proteins		
ILK **Integrin-linked kinase** *ITGB1BP2* **Melusin**		Severe dilated cardiomyopathy (Ref. 118). One patient with dilated cardiomyopathy (Ref. 119)
PARVA/PARVB/PARVG **Parvin**	–	
PINCH1/PINCH2 **PINCH**	Early onset LGMD	LGMD2W: caused by mutations in the LIMS2/ PINCH2 gene. Childhood onset LGMD with macroglossia and calf enlargement. Development of decreased ejection fraction with global left ventricular dysfunction in 3rd decade of life, and severe quadriparesis with relative sparing of the face, but characteristically a broad based triangular tongue (Ref. 117)
PTK2 **FAK**		FAK deficiency in cells contributing to the basal lamina results in cortical abnormalities resembling congenital muscular dystrophies (Ref. 163)
FERMT1, 2 and 3 **Kindlin 1, 2 and 3**	–	Mutations in kindlin 1 and 3 found in patients affected by skin and immune disorders respectively (Refs 164, 165)
3.2. Desmin network via plectin		
DES **Desmin**	Limb-girdle myopathy, distal myopathy or both	LGMD1E, also known as dilated cardiopathy type 1F: dilated cardiomyopathy and conduction defects together with progressive proximal muscle weakness (Ref. 166) LGMD2R: Young adult-onset of progressive LGMD with mild facial muscle weakness but severe limb weakness. Incomplete right bundle branch block and rare ventricular extrasystoles reported (Ref. 133) Myofibrillar myopathy: age of onset between 10 and 61 years. The distribution of weakness is distal or both proximal and distal. Muscle atrophy, mild facial weakness, dysphagia, dysarthria and respiratory insufficiency can occur (Refs 126, 134) Dilated cardiomyopathy type 1I (Ref. 167) Scapuloperoneal syndrome, neurogenic, Kaeser type (Ref. 168)
PLEC1 **Plectin**	Childhood onset proximal myopathy, in which the skin may or may not be involved	LGMD2Q: Early childhood onset of proximal muscle weakness and atrophy without skin involvement. No cardiac or respiratory involvement, and intelligence is normal (Ref. 135) Epidermolysis bullosa simplex with muscular dystrophy (Ref. 169) Epidermolysis bullosa simplex, Ogna type (Ref. 170) Epidermolysis bullosa simplex with pyloric atresia (Ref. 171)
3.3. Proteins potentially associated with costameres		
FRG1 **Protein FRG1**		To date, no mutations in the gene FRG1 have been reported to cause muscular dystrophy; FRG1 transgenic mice develop muscular dystrophy with features characteristic of the human disease (Ref. 136), but its relevance in the pathogenesis of FSH is still uncertain

α−ε, sarcospan, syntrophins α1, β1 and β2, and two isoforms of a subsarcolemmal protein, α-dystrobrevin-1 and -2) that form a complex for binding cytoplasmic myofibrillar contractile elements and proteins of the extracellular matrix, providing structural support to the sarcolemma (Refs 50, 51). Other more peripheral components of the complex include neuronal nitric oxide synthase (nNOS), caveolin-3 and laminin α−2 (Refs 42, 52).

In the relation to the DGC complex, three subcomplexes can be identified, on the basis of different biochemical characteristics and localisation: the

sarcoplasmic sub-complex, the sarcoglycan (transmembrane) complex and the dystroglycan subcomplex (Ref. 53).

The sarcoplasmic subcomplex. This is composed of proteins present in the sarcoplasm of muscle fibres, mainly dystrophins, dystrobrevins and syntrophins.

Dystrophin. Dystrophin is a cytoskeletal protein found on the inner surface of the sarcolemma of skeletal muscle (Ref. 54, 55, 56). Its amino-terminal residue is a cytoplasmic actin-binding domain, whereas the C-terminal domain is associated with a transmembrane complex of glycoproteins called dystrophin-associated glycoproteins (DAGs), some of which interact directly with elements of the extracellular matrix (Ref. 43). Absence or dysfunction of dystrophin leads to an increase in the fragility of the membrane, in turn, weakening the transmission of mechanical forces through the sarcolemma. The result is myofibrillar necrosis, leading to a succession of cycles of degeneration and regeneration, exhausting the regenerative capacity of the muscle. This is accompanied by a loss of myofibrils, muscle being replaced by fibrous and fatty tissue, as observed in patients with Duchenne and Becker muscular dystrophies.

Dystrobrevins. Dystrobrevins are expressed in various types of tissue, including the brain and muscle. The α-dystrobrevin isoform is expressed in muscle and is homologous to the cysteine-rich C-terminal domain of dystrophin (Refs 57, 58). This isoform is directly associated with dystrophin and the sarcoglycan complex (Refs 59, 60). Nevertheless, to date, no myopathies have been described secondary to mutations in the α-dystrobrevin gene (Ref. 61), although some cases of left ventricular noncompaction-1 have been reported (Ref. 62) (Table 1).

Syntrophin. Syntrophins are a family of cytoplasmic membrane-associated adaptor proteins directly associated with dystrophins and related proteins (Ref. 63). They serve as a link between the extracellular matrix and the intracellular downstream targets and cell cytoskeleton by interacting with F-actin. They play an important role in regulating the postsynaptic signal transduction, sarcolemmal localisation of nNOS, EphA4 signalling at the neuromuscular junction, and G-protein-mediated signalling (Ref. 64). There are three isoforms encoded by different genes expressed in muscle: α−1, β−1 and β−2 (Refs 65, 66). To date, only one type of heart disorder (long QT syndrome) related to mutations in these genes has been described, this being attributable to an α−1 syntrophin mutation (Ref. 67).

Sarcoglycan subcomplex. Sarcoglycans are glycosylated proteins with a transmembrane domain (Ref. 68) that needs to be correctly assembled in a complex together with dystrophin (Ref. 69) to maintain the sarcolemma (Refs 70, 71). The sarcoglycan subcomplex is composed of the α, β, γ, δ, ε and ζ-sarcoglycan transmembrane proteins (Refs 50, 72), of which α and δ-sarcoglycans are only expressed in muscle tissue, whereas the rest are more widely distributed (Ref. 73). This complex has two functions: on the one hand, it has mechanical and non-mechanical roles in the interaction between the extracellular matrix, sarcolemma and cytoskeleton (Ref. 74); and, on the other hand, it mediates membrane targeting and the stabilisation of the sarcospan protein. When mutations result in partial or total loss of sarcoglycans α, β or γ, sarcospan is also affected (Ref. 75). Four types of autosomal recessive limb-girdle muscular dystrophies have been described secondary to mutations in genes that code for components of this complex (Ref. 76) (Table 1).

Dystroglycan subcomplex. Dystroglycans include two proteins that are part of a complex of glycoproteins associated with dystrophin. They are both coded by the same gene, *DAG1* (Ref. 77), which, after post-translational processing, produces a transmembrane protein, β-dystroglycan and an extracellular protein, α-dystroglycan.

The dystroglycan complex strengthens the physical connection between the cytoplasmic proteins that bind to the actin cytoskeleton and components of the basement membrane, proteins of the extracellular matrix that contain globular domains of laminin (for example, laminin, agrin and neurexin) (Refs 77, 78).

Although genetic dystroglycan deficiency leads to muscular dystrophy with cognitive impairment (Ref. 79), several forms of congenital muscular dystrophy are the result of abnormalities in the glycosylation of mucin-like domains of α-dystroglycan, essential for its correct functioning as a receptor of the extracellular matrix in various types of tissue, including skeletal muscle and brain (Refs 78, 80) (Table 1).

The vinculin–talin–integrin system

Vinculin and talin are two cytoskeletal proteins that are essential for the linkage of actin filaments to the plasma membrane (Ref. 81), whereas integrins are heterodimers composed of two subunits, α and β (Ref. 82), involved in the cascade of intracellular signalling (Ref. 83).

Vinculin. Vinculin is associated with the cytoplasmic side of the plasma membrane, interacting with talin and α/β-catenins (together with cadherin) (Ref. 84, 85, 86). In addition, there is evidence to suggest that vinculin plays a critical role in the regulation of integrin clustering, force generation and strengthening of adhesion (Ref. 87). Mutations in the gene that codes for vinculin lead to dilated cardiomyopathy type 1W and to familial hypertrophic cardiomyopathy-15 (Refs 88, 89), but have not yet been found to cause disorders affecting skeletal muscle (Table 1).

Talin. Talin is a dimeric protein that contains different domains for binding to the β-integrin subunits, F-actin, Wech, H-Ras, layilin, PIPK, focal adhesion kinase (FAK), actin, vinculin and muscle-specific α-synemin (Ref. 90). Hence, talin links integrins with cytoskeletal actin (Ref. 91), being essential for the structural integrity of the attachment of cells to the extracellular matrix (Ref. 92). As well as this structural function, talin modulates ligand binding to integrins and is involved in signal transduction, recruiting signalling proteins, such as FAK and phosphatidylinositol-(4)-phosphate 5-kinase type Iγ (PIPKIγ) to focal adhesions. Talin is coded by two genes that code for two isoforms (Tln1 and Tln2), with 74% sequence identity. Tln 1 is ubiquitous while Tln 2 is expressed in fewer tissues, mainly the heart, brain and skeletal muscle (Ref. 91). No disorders are known to be associated with mutations in either of these isoforms.

Integrin. The vinculin–talin–integrin system includes various transmembrane heterodimeric receptors that play a very important role in cell adhesion (Ref. 82). They link the extracellular matrix to the actin cytoskeleton and facilitate the bidirectional transmission of signals between the extracellular matrix and the cytoplasm (Refs 83, 93).

Integrins are connected to actin filaments through talin, vinculin and other related proteins, such as α-actinin, integrin-linked kinase (ILK), filamin and tensin (Ref. 94). As well as their structural function, integrins recruit signalling proteins for the transduction of mechanical stimuli through FAK, melusin, paxillin, src, cas and PIPKI (Ref. 95).

Integrins play an important role in the process of muscular differentiation and, in particular, are mediators of cell adhesion and migration (Ref. 6). Various different heterodimers have been identified, composed of α and β chains. The α/β combination determines the binding specificity of the ligand of the integrin heterodimer for various different proteins of the extracellular matrix, including fibronectin, laminin and collagens. The most common isoforms in skeletal muscle of adults are α7B and β1D, the latter being found with vinculin in skeletal and cardiac muscle (Refs 96, 97). The affinity of integrin for its ligands depends on its activation, this usually occurring through the cytoplasmic tail of β-integrins that can be regulated by various biochemical signalling pathways (Ref. 98).

During myogenesis, two isoforms of integrin 1β are expressed. The isoform 1A is expressed in myoblasts and is under-expressed during tissue formation, whereas isoform 1D is expressed during fusion and its expression increases during the maturation of myotubes, completely displacing the isoform 1A in mature myotubes (Ref. 96).

Two types of congenital muscular dystrophy have been found to be because of mutations in genes coding for integrins, one to mutations in *ITGA7* (Ref. 99), and the other, to mutations in *ITGA9* (Ref. 100) (Table 1).

On the other hand, as previously mentioned, integrins interact with collagens and it is worthwhile to underline that collagen VI plays a fundamental role in costameric function maintenance, given that proteins essential for mechanotrasduction are altered in collagen VI null mice and collagen VI myopathy (Refs 101, 102, 103, 104, 105) (Table 1).

Other proteins associated with costameres

As well as the aforementioned complexes, other proteins are indirectly involved in the structure of the costamere, either by being associated with integrins, or by being part of or associated with IFs.

Integrin-associated proteins. These include a complex formed by ILK, particularly interesting cysteine- and histidine-rich protein (PINCH) and parvin, the IPP complex (Ref. 106).

Regarding the proteins in the IPP complex, ILK regulates integrin-mediated signalling, and PINCH and parvins are adaptor proteins. ILK was identified in 1996 among other proteins that bound to the cytoplasmic region of integrin β1 (Ref. 107). It is a serine–threonine protein kinase that, as well as binding to PINCH and parvins, also binds to the cytoplasmic regions of integrins β1 and β3, regulating integrin-mediated transduction signal (Refs 107, 108). PINCH has two isoforms, PINCH1 and 2 (Refs 109, 110) and together with ILK, is essential for controlling the change of shape, mobility and survival of cells (Ref. 111). Parvins are a family of proteins composed of α-parvin (also known as actopaxin and calponin homology-containing ILK-binding protein), β-parvin (affixin) and γ-parvin that bind to ILK through a calponin-homology domain (Refs 112, 113, 114).

Another integrin-associated protein is melusin, a protein coded by the *ITGB1BP2* gene. Melusin binds to the cytoplasmic domain of the integrin β1 subunit in costameres, acting as a specific biomechanical sensor of signal transduction (Ref. 115). In the cardiac muscle, the effect of melusin is to prevent heart failure under biomechanical stress (Ref. 116).

Some mutations in the genes coding for proteins of this complex have been associated with muscular dystrophies (Ref. 117) and with heart disease (Refs 118, 119), (Table 1).

Another protein closely associated with integrins is FAK. The phosphorylation of this protein activates hypertrophic signalling through Akt, extracellular signal-regulated kinase 1/2 and Jun N-terminal kinase/c-Jun pathways. The FAK signalling pathway regulates the expression of MEF2 transcription factors, which in turn regulate the expression of sarcomeric proteins (Ref. 120) and it has been confirmed that FAK inhibition results in an abnormal maturation of costameres and myofibrils (Ref. 121).

Finally, kindlin is a protein that binds directly to β-integrins and ILK. It has three isoforms (kindlin 1, 2 and 3) in vertebrates, although the most widely expressed isoform in cardiac and skeletal muscle is kindlin 2 (Ref. 122). Kindlin is found at costameres and plays an important role in myoblast differentiation in vitro (Ref. 123).

Desmin and Plectin. Desmin is the most important protein in IFs for the organisation of the costamere in the muscle (Ref. 124). It surrounds Z-discs and links the contractile apparatus with the sarcolemma, cytoplasmic organelles and the nucleus (Ref. 125) providing structural solidity and integrity to the cell during force transmission and mechanochemical signalling (Ref. 126).

Plectin, a protein associated with the cytoskeleton, is abundantly expressed in various types of tissue and cell types (Refs 127, 128). It has been suggested that it may interact directly with actin filaments, microtubules, microtubule-associated proteins, α-spectrin, and integrin β4, as well as most IFs (Refs 129, 130, 131).

Myofibre integrity depends on the desmin network targeting Z-discs and costameres via plectin isoforms. Among the different isoforms of plectin, 1 and 1f are localised at costameres. Plectin deficiency results in desmin detaching from Z-discs, costameres, mytochondria and nuclei; depending on which plectin isoform is lacking, desmin aggregates have a distinct morphology and form in distinct cytoplasmic compartments (Ref. 132).

Desmin deficiency leads to limb-girdle muscular dystrophy, LGMD2R (Ref. 133) and an allelic variant of myofibrillar myopathy (Ref. 134), whereas plectin deficiency produces LGMD 2Q (Ref. 135) (Table 1).

Protein potentially associated with costameres. Facioscapulohumeral muscular dystrophy region gene 1 (FRG1) protein is one of a group of proteins whose localisation and function are still to be clearly defined. There is evidence that it participates in the processing of RNA (Ref. 136) and it may be involved in F-actin bundling in *Caenorhabditis elegans* (Ref. 137). It has been suggested that FRG1 in *C. elegans* is a multi-function protein present in various subcellular niches, but primarily in nucleoli and dense bodies. In this organism, the most important function of dense bodies is transduction of mechanical forces, essentially by anchoring sarcomeric actin to the extracellular matrix; that is, they are structures with a similar function to that of the combination of Z-discs and costameres in vertebrates (Refs 137, 138). Therefore, as well as in *C. elegans*, FRG1 could be involved in costameres in vertebrates.

Summary

The structure and role of costameres and their involvement in the pathophysiology of skeletal muscular disorders are still not well understood. Given that this system includes many molecules closely associated spatially and with two types of function (structural support and signal transduction), it is likely that abnormalities in any of the components have an impact on the stability of the whole system, with consequences for the structure of the membrane, or the functionality of the contractile apparatus, or both at the same time. This has been confirmed in dystrophinopathies, in which the absence of dystrophin leads to the disappearance of dystoglycans/sarcoglycans, and in sarcoglycanopathies, in which the lack of the protein as a result of mutation leads to a secondary reduction or disappearance of the remaining sarcoglycans. Moreover, a similar phenomenon has also been reported when contactin-1 gene is mutated, as this results in reduced expression of β2-syntrophin and α-dystrobrevin (Ref. 139).

Regarding potential therapies for myopathic processes because of defects in costamere proteins, different approaches have been widely tested. However, clinical trials have only been performed for a few of them. In the case of Duchenne muscular dystrophy (DMD), for example, molecular-based pharmacologic therapies to correct gene products have been applied (Refs 140, 141). In sarcolgycanopathies, an adeno-associated virus has been used to transfect the exogenous gene (Ref. 142) and in collagen VI myopathies, compounds that modulate the activity of the mitochondrial permeability transition pore have been assessed (Refs 143, 144). Unfortunately, just a few of these approaches showed the sought outcome so far.

Further research is required on selective silencing and at different stages in the processes of myogenesis and differentiation of skeletal muscle in physiological and pathological conditions to clearly establish the role of these structures in skeletal muscle. Current knowledge suggests that these proteins could be therapeutic targets for preventing the 'de-structuring' of the sarcolemma that leads to the degeneration of myofibres in patients with muscular dystrophy.

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